Patient participation in pharmacovigilance

Leàn Rolfes

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General Introduction

PHARMACOVIGILANCE AND SPONTANEOUS REPORTING SYSTEMS

In recent years, patient participation in the surveillance of the safety of drugs used in daily practice, has become more important. Pharmacovigilance, as defined by the World Health Organization (WHO), includes *the detection, assessment, understanding and prevention of adverse effects or any other drug related problems* [1]. Before drugs are marketed, they undergo extensive risk assessment, including clinical trials [2]. Due to the design of pre-marketing clinical trials, i.e. small and homogeneous highly selected populations monitored for short periods of time, not all possible adverse drug reactions (ADRs) are detected. Once a drug is used more widely and under more diverse conditions additional ADRs can be identified, for example due to concurrent use with other drugs or medication errors [3]. Patient participation in this context means that patients provide first-hand information about their experiences of ADRs, without the filter or the interpretation of a healthcare professional. This can yield valuable information for pharmacovigilance [4].

Rise of spontaneous reporting systems

The first systematic international efforts to address drug safety issues were made after the thalidomide disaster (*Softenon*®, *Distaval*®) [5]. Thalidomide was marketed as a sleeping pill and anti-emetic. It was promoted for use in pregnant women in over 20 countries between 1956 and 1961. At that time, many thousands of congenitally deformed infants were born as the result of exposure in utero to an unsafe drug [1]. This tragedy highlighted the importance of systematic surveillance of drug safety after a drug entered the market. It caused a shift in drug safety worldwide from reactive to proactive actions. It led to the establishment of committees on the safety of drugs in many countries; for surveillance of drug safety before marketing as well as postmarketing pharmacovigilance [5,6].

One of the initiatives to monitor the safety of drugs in the postmarketing phase was establishing spontaneous reporting systems, to which ADR observed in daily practice could be reported voluntarily. The spontaneous reporting systems are mainly operated by national pharmacovigilance centres. These centres are generally part of the drug regulatory authorities and are usually funded (partially) by user fees paid by the pharmaceutical industry or relevant government health department. Some centres, for example in the Netherlands and New Zealand, are independent organizations working in close collaboration with the drug regulatory authority [7].

In 1968, the WHO set up the WHO Programme for International Drug Monitoring (PIDM) in order to systematically collect information on serious ADRs during the development and particularly after drugs have been made available for public use. WHO PIDM members can transmit their reports to the WHO global database for

ADR reports, VigiBase, which is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (WHO-UMC) [8]. Initially the WHO PIDM members consisted of 10 countries. As of January 2016, 123 countries have joined the WHO PIDM, and in addition 28 associate members are awaiting full membership [8]. In 2017, VigiBase contained over 15 million reports [9].

In the European Union (EU), the process of pharmacovigilance started with the first European Commission medicines legislation in 1965 and the initial introduction of ADR reporting schemes in some European countries. In 1995, the European Agency for the Evaluation of Medicinal Products (EMEA) has been established, since 2004 called the European Medicines Agency (EMA), in order to have a closer cooperation between EU member states [10,11]. The legal provisions for pharmacovigilance in the EU have already been enhanced twice, first in 2004, when the risk management approach was introduced, and in 2010, when specific legislation was passed to strengthen pharmacovigilance in the EU. This new legislation (Regulation No 1235/2010), in force since July 2012, presents major changes, for example the inclusion of patients as stakeholders in pharmacovigilance [11,12]. In the EU, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing all aspects of the risk management of therapeutic effects of medicinal products. This includes the detection, assessment, minimisation and communication of ADRs [13]. The Committee includes members appointed by the EU member states and the European Commission. In 2016, EudraVigilance, the pharmacovigilance database of the EMA, contained over 10 million reports of possible ADRs sent by pharmacovigilance centres and marketing authorization holders (MAH) within the European Economic Area (EEA) [14].

ADR reporting and signal detection

Pharmacovigilance centres receive ADR reports through telephone, paper or electronic reporting forms [7]. Most centres collect and analyse their data on a national level. The primary aim of spontaneous reporting systems is to timely detect new drug safety issues. A signal is defined as *information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action* [15]. Collecting real life data enables to identify whether harms outweigh benefits. Consequently, regulators have to take necessary actions to protect patient safety [16]. The advantage of case reports and case series is that they have a high sensitivity for detecting novelty. They permit discovery of new diseases and unexpected effects (adverse or beneficial) as well as

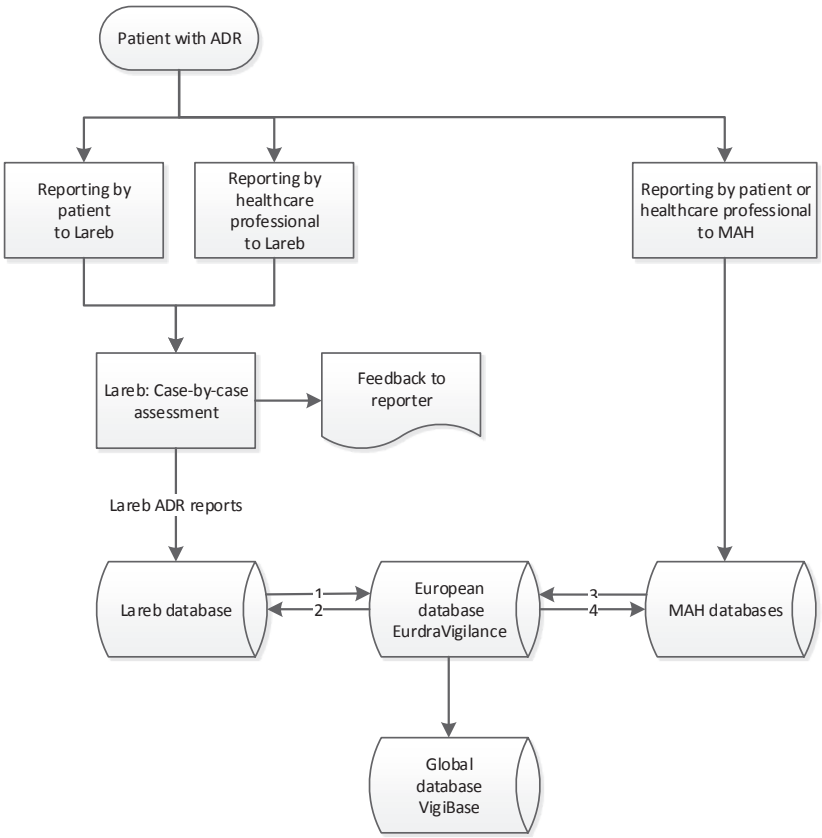
the study of mechanisms, and they play an important role in medical education [17]. Currently, the three primary post marketing drug safety evidence sources include spontaneous reports, clinical trials, and observational studies. It was demonstrated in studies in Europe (2012-2013) and the USA (2007-2009) that the majority of new drug safety signals were triggered by spontaneous reports [18,19].

Methods applied for signal detection can be qualitatively by review of individual or series of ADR reports, also called 'case-by-case' analysis, or quantitatively using statistical techniques. During a case-by-case assessment, the clinical-pharmacologic aspects of the drug-ADR associations are mostly used as primary trigger for signal detection. Mainly for large spontaneous reporting schemes, such as the Yellow Card Scheme in the UK, large volume of reports make it impractical to evaluate every report in detail. Statistical methods are therefore applied as a first step of signal detection [20]. Pharmacovigilance centres analyse their data and store them in their national ADR database, or/and transfer them to VigiBase and EudraVigilance. These latter databases allow analysis on a more aggregated level.

Pharmacovigilance using the spontaneous reporting system in the Netherlands

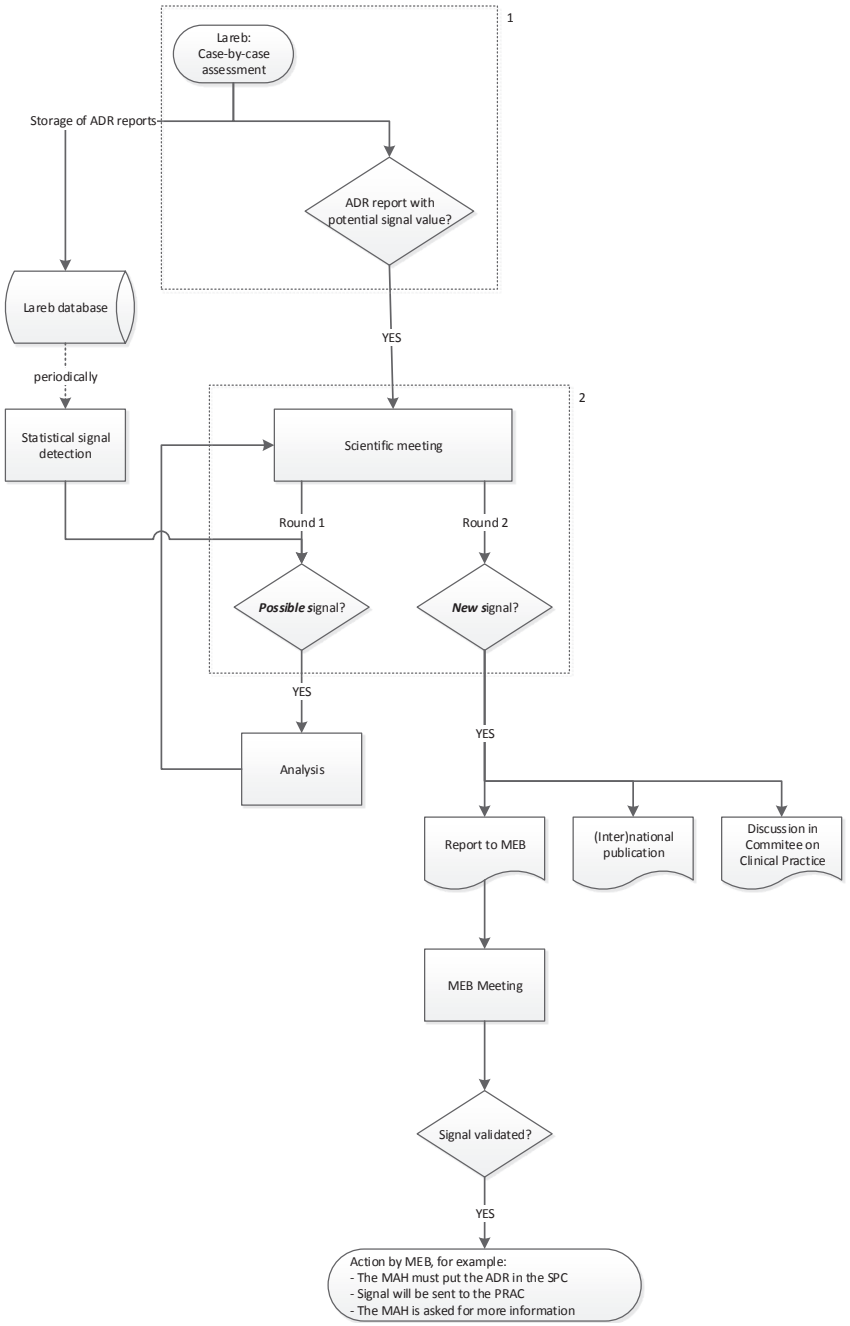
The start of pharmacovigilance in the Netherlands goes back to 1963, when the Medicines Evaluation Board (MEB) was funded [21,22]. Also in this year, the Royal Dutch Medical Association joined the government in setting up a spontaneous reporting systems for ADRs. In 1965, the task for maintaining this reporting system was taken over by the National Drug Monitoring Centre (Bureau Bijwerkingen Geneesmiddelen), which was part of the Dutch Healthcare Inspectorate. An initiative of a group of pharmacists that found that pharmacovigilance needed greater awareness led to the establishment of the Netherlands Pharmacovigilance Centre Lareb in 1991. In 1995, the Dutch government decided to restructure the pharmacovigilance system in the Netherlands, and the Netherlands Pharmacovigilance Centre Lareb became the designated national centre for all reports of suspected ADRs concerning registered drugs. In 2011, this task was extended with the surveillance of the safety of vaccines and drug exposure during pregnancy.

Lareb is an independent foundation funded by the Ministry of Health and works in close collaboration with the Dutch MEB [23]. She receives reports of possible ADRs from healthcare professionals, MAHs, and since 2003 also from patients. All reports are stored in the Lareb database, which contained almost 200,000 reports in 2017. There is data exchange with the MAHs, who have systems to monitor the safety of their marketed drugs, VigiBase and EudraVigilance. Each incoming ADR report undergoes a case-by-case assessment. After this assessment, a feedback is sent to the reporter in response to their reported ADR (Flowchart 1).



Flowchart 1. *Process of reporting and assessment of ADRs at the Dutch pharmacovigilance centre and exchange with (inter)national databases*
1: Lareb ADR reports replica shared
2: Retrieval of Dutch MAH ADR reports
3: MAH reports replica shared
4: Retrieval of Lareb reports for MAH's specific drugs

Signal detection is carried out during the case-by-case assessment. In addition, a statistical screening is carried out periodically for signals, nowadays based on a prediction model that takes into account disproportionality of the association in the database, Naranjo score for causality, and the proportion of reports of healthcare professionals and MAHs [24]. When new drug safety signals are detected, these are discussed with the Clinical Advisory Board, which consists of clinical doctors and hospital pharmacists. Lareb informs the MEB about all new drug safety issues. The MEB is the authority responsible to take decisions on regulatory actions, for example changes in the product's Summary of Product Characteristics (SPC). Due to the European approach of drug regulation, some signals are sent to the PRAC of the EMA [23,25]. In order to stay up to date with knowledge and experiences in clinical



Flowchart 2. *Process of signal detection and dissemination at the Netherlands Pharmacovigilance Centre Lareb*

Whenever the answer to a decision is 'No' there is no further action

1: First step of signal detection during case-by-case assessment

2: Decisions about the possible signals are made during the weekly scientific meeting

practice, the MEB has a Committee on Clinical Practice. Members include doctors, pharmacists, pharmacist assistants and nurses [26]. Whenever Lareb has a potential signal based on topics like drug quality issues, naming issues of drugs, off-label use, problems with interchangeability between drugs, these can be discussed in this Committee on Clinical Practice. In order to inform all stakeholders in pharmacovigilance, Lareb actively communicates about drug safety signals and many signals are also published in both journals for healthcare professionals and patients (Flowchart 2). In addition to signal detection at the Dutch pharmacovigilance centre, the Dutch Drug Regulatory Authority and the MAHs also have systems to carry out signal detection.

THE PATIENT'S ROLE IN PHARMACOVIGILANCE

Patient participation has not always been common in pharmacovigilance practices. Due to concerns that patients may lack medical knowledge and would therefore probably not be able to make high quality reports, reporting of possible ADRs was mainly reserved for healthcare professionals [5]. In the past, only a few countries allowed patients to report their drug concerns directly to the national pharmacovigilance centre, among which Australia since 1964 and the USA since 1969 [7,27].

Over the years there was a change in attitude in which the patient's experiences are valued. The 2000s saw a dozen countries implement patient reporting systems, with Denmark and the Netherlands being the first European countries in 2003, followed by Italy in 2004, the UK in 2005 and Sweden in 2008 [7,15]. Also outside Europe countries were making efforts to accept reports directly from patients, for example Malaysia in 2007 and the Philippines in 2008 [7,27].

In Europe, the role of patients as stakeholders in pharmacovigilance became official after the implementation of the pharmacovigilance legislation (Regulation No 1235/2010) in July 2012. This legislation enabled patients throughout the EU to report their drug concerns directly to the national centre [28,29]. In addition, since 2012 patients have a representative as full member of the PRAC [30]. The patient representative plays an invaluable role in ensuring that regulators remember to take the patient's perspective into account. They also contribute to decisions about the wording and timing of risk communications, which play a fundamental role in ensuring drug safety [30].

EXPERIENCES WITH PATIENTS AS REPORTERS IN PHARMACOVIGILANCE

A healthcare professional may directly notice an ADR or he/she can learn about it after discussing it with the patient. After taken his/her own experiences and knowledge

into consideration, a healthcare professional can consider to report an ADR. Reports from healthcare professionals are important in order to find new drug safety information. However, only part of the patient's story may be reported by the healthcare professional. Direct patient reporting of ADRs may provide first-hand information and could therefore be an important contribution to pharmacovigilance.

There are many studies that explored the contribution and impact of patient reporting in pharmacovigilance. Patient reporting has many different aspects and not all of them have been studied yet. Most studies explored the type of ADR as reported by patients compared to healthcare professionals. In addition, some explored the nature of the ADR, the quality of reported information and the contribution of patient reports to signal detection. An overview of the most important topics addressed in literature are presented in Table 1, Column: *Has this topic been explored?*

The type of ADR reported by patients

The type of ADR reported by patients has mostly been explored on a broad system organ class level, for example 'gastrointestinal disorders' or 'cardiac disorders' [31-38]. Some studies looked into the reported ADR on a more specific level and demonstrated that the ADRs most frequently reported by patients versus healthcare professionals have similarities and differences [33,36,38]. For example, in the UK, nausea and headache were the two most reported ADRs by patients as well as healthcare professionals. Tiredness, suicidal ideation and joint pain were in the list of top 20 most frequently reported ADRs by patients, but not in that of healthcare professionals [36]. In the Netherlands, the five most reported ADRs were comparable between patients and healthcare professionals, however the ranking differed between both groups [33]. Patients reported myalgia most frequently, while for healthcare professionals this ADR ranked fourth. Additionally, it seemed that patients reported on symptoms that may be less easy to discuss with the healthcare professional, for instance those relating to sexual matters or weight gain [31,33].

The nature and quality of information reported by patients

Some studies investigated information characterising the ADR as reported by patients. Examples are the time course of the ADR, information about drug use and treatment, and the impact of the ADR on the patient's daily life. Studies demonstrated that patients are capable to provide a detailed description of the ADR. An example for this is the outcome of the ADR. A study in the Netherlands demonstrated that the outcome of the ADR was reported in over 85% of all patient reports versus 68% of healthcare professionals [33]. Concerning the type of outcome, it is interesting that patients reported non-recovery of the ADR more often compared to healthcare professionals [33,36,40,41]. Additionally, it was mentioned that patients can generally provide

Table 1. *Current status of what is known about direct patient reporting of ADRs to pharmacovigilance centres*

Topic	Has this topic been explored?	What is known from literature?	What is missing?
The type and nature of reported ADR	• Many studies [32-36,38,40-42,44,46] • Most explored: directly measurable information, e.g. the seriousness of the ADR [32-36,40,41,44,46] • Less explored: content of information [36,40,42]	• Positive towards patient reports concerning directly measurable information • Patients give a detailed description of the ADR and the impact on their daily life. This information is less likely to be reported by HCPs	• Full scale of information reported by patients, including information provided in open text fields • Comparison between patients and separate groups of HCPs instead of all HCPs together
The quality of reported information	• Many studies explored technical completeness of reported information [31,33-36,40-42,44-48]	• Completeness of information: positive towards patient reports	• The quality of relevant clinical information reported by patients
The contribution to signal detection	• Some studies explored the contribution of patient reporting to signals in general [20,49-51] • Few studies explored whether patient reporting contributes to earlier signal detection [50,58]	• Reports from patients are included in (potential) signals • Different potential signals were identified when the database was screened for reports of patients and HCPs combined and separately • Reports of patients have the potential to contribute to early signal detection	• Whether reports by patients contribute to the early detection of new signals • Whether reports by patients contribute differently to several kind of ADRs, e.g. serious versus non-serious
Practice of pharmacovigilance in terms of feedback for patients	• Explored in few studies [7,59,60]	• Only few countries send personalized feedback to patients (e.g. New Zealand, Malaysia, Australia and the Netherlands) • Patients want feedback from a pharmacovigilance centre, e.g., how common the ADR is	• What kind of feedback fits best to the patient's needs; general or personalized • Whether patients are satisfied with feedback received in response to their reported ADR.

HCPs = healthcare professionals

much richer descriptions of behavioural phenomena and feelings than healthcare professionals. Patients are generally better in explaining the nature, significance and consequences of ADRs than healthcare professionals [42]. An example is the impact of the ADR on the patient's daily life. In the UK, 44.8% of patients reported that the suspected ADR was severe enough to affect everyday activities, for 15.4% the ADR was uncomfortable or nuisance, and for only 2.6% the ADR was mild or slightly uncomfortable [36]. Patients are also more likely than healthcare professionals to report about this aspect of ADRs [36,39,42,43]. In the Netherlands, the impact of the ADR on patient's daily life was reported in 17% of reports coming from patients compared to 2% of healthcare professionals [39].

The quality of information in patient reports has been studied in many studies in terms of technical completeness of reported information [31,33-36,40-42,44-48]. These studies were overall positive about patient reporting. To our knowledge there is no information specifically addressing the quality of clinical information reported by patients.

Contribution of patient reports to signal detection

Studies demonstrated that there is an upward trend in the contribution of patient report to signal detection [20,49-51]. In the UK, the proportion of signals for which ADR reports from patients contributed increased from 15.6% in 2009 to 23.6% in 2010 [49]. In the Netherlands, the pharmacovigilance centres started to accept patient reporting in 2003. The number of reports directly from patients in the signals rose from 16 (10% of total) in 2010 to 161 (28.3% of total) in 2015.The proportion of all patient reports present in the Lareb database that led to a signal was relatively stable over the years, average of 2.0%, compared to 4.2% of healthcare professional reports [52]. Some examples for which reports by patients have been the key in identifying are: *thyroid dysregulation after packaging change of a levothyroxine preparation from a bottle to a blister* [53,54], *SSRIs and aggression* [55], *vitamin B6 and polyneuropathy* [56], and *persistent hair loss and the use of docetaxel* [57]. A retrospective analysis of spontaneous reporting of ADRs in the UK's Yellow Card Scheme furthermore demonstrated that different signals of disproportionate reporting could be found when the database was screened for healthcare professional and patient reports combined and separately [20]. After combining the patient and healthcare professional reports, 278 (11%) signals of disproportionate reporting identified when each group was analysed separately were no longer found, including 12 potentially serious ADRs not listed on the product's SPC. On the other hand, the combined dataset identified an additional 508 signals of disproportionate reporting that were not identified when patient or healthcare professional reports were analysed separately. Approximately 10% of these signals of disproportionate reporting were assessed as serious ADRs and were not listed on the product's SPC.

GAPS IN KNOWLEDGE

Over the years, pharmacovigilance centres gained experience with patients as key stakeholders in pharmacovigilance. Despite all positive experiences and efforts that have been made to explore how they could add value to pharmacovigilance, there is still a gap in knowledge about the actual impact of direct patient reporting on pharmacovigilance. This thesis focussed on four main topics, namely (i) information related to the nature of the reported ADR, (ii) the quality of reported information, (iii) the contribution to signal detection, and (iv) practice of pharmacovigilance in terms of feedback for patients. Table 1 provides a brief overview of what is already known about patient reporting in literature and information still missing. These previously unexplored topics led to the specific study objectives as described in the studies of this thesis.

AIM AND OUTLINE OF THE THESIS

Aim of the thesis

The aim of this thesis is to explore the impact of patient participation on pharmacovigilance.

Outline of the thesis

This thesis includes six studies divided over four chapters, followed by a general discussion on the implications of our research.

Chapter 2 focusses on the type of information reported by patients compared to that reported by healthcare professionals. Chapter 2.1 studies the views of different types of reporters and assessors of ADRs, on what they consider important information regarding an ADR report, using a quantitative analysis. Based on this information, Chapter 2.2 quantitatively compares information reported by patients and healthcare professionals. From findings in literature and the study presented in Chapter 2.2 it was demonstrated that patients more often than healthcare professionals report about the impact of ADRs on their daily life. In Chapter 2.3 an electronic survey was used to ask patients who reported an ADR about the impact of the ADR on their health related quality of life.

Chapter 3 compares the quality of relevant clinical information reported by patients and healthcare professionals.

Chapter 4 provides insight in the difference in time to reporting ADRs that led to drug safety signals between patients and healthcare professionals. For this study there was a collaboration with the WHO-UMC.

Chapter 5 focusses on the practice of pharmacovigilance. It explores patient's satisfaction and expectations towards feedback from the pharmacovigilance centre in response to their reported ADR, using an electronic survey.

Chapter 6 presents a general discussion in which the benefits and consequences of patient participation in pharmacovigilance are discussed. Finally, we come with some practical recommendations and areas for future studies in order to strengthen the field of pharmacovigilance.

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2

Nature of information reported by patients

2.1

Important information regarding reporting of adverse drug reactions: a qualitative study

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ABSTRACT

Objective: To give an overview of the views of different types of reporters (patients and healthcare professionals) and assessors of adverse drug reactions (ADRs) on what they consider important information regarding an ADR report.

Methods: A semi-structured interview was conducted among reporters and assessors of ADRs in the Netherlands. All interviews were audiotaped and transcribed verbatim. Content analysis was used on the data. All transcripts were coded individually by two researchers. A list was drafted of all elements of information mentioned during the interviews.

Key findings: In total 16 interviews were conducted. Elements of information that were explicitly brought up during the interviews were the impact of the ADR on the patient's daily life and information regarding causality. Furthermore, the correctness of reported information was found important by assessors of ADRs. Generally, patient reporting was seen as a very positive development for pharmacovigilance.

Conclusion: Patients reported that the severity of ADRs and their impact on daily life were important subjects. In the interviews with healthcare professionals, either reporters or assessors, the focus was mainly on causality. The correctness of the given information is considered by ADR assessors to be very important. Regarding patient reporting the overall view was positive. Because healthcare professionals and patients have different views regarding ADR reporting, in daily practice it is important to receive reports from both groups to assess the true nature of the ADR.

INTRODUCTION

A pharmacovigilance centre collects reports of possible adverse drug reactions (ADRs) in order to detect ADRs in the post marketing phase. In the past the reporting of ADRs was restricted to healthcare professionals in many countries. Nowadays more countries allow patients to report ADRs directly and patient reporting is seen as an increasingly important topic in pharmacovigilance [1]. Patient reporting is also introduced in the new European pharmacovigilance legislation [2]. This introduction indicates a change in attitude in which the patient's experience is valued [1].

The contribution of direct patient reporting to pharmacovigilance has been explored in a number of studies [3,4]. Patients and healthcare professionals views on ADRs and motives for reporting ADRs can differ. This may result in the reporting of different kinds of information. Little is known about what kind of information different stakeholders in pharmacovigilance actually consider important when it comes to ADR reporting.

The aim of our study is to give an overview of views of different type of reporters (patients and healthcare professionals) and assessors of ADRs on what they consider important information regarding an ADR report.

METHOD

This qualitative study used semi-structured interviews to capture reporters view on what they consider important information regarding an ADR report. Patients, general practitioners, pharmacists, and medical specialists were selected at random from the database of the Netherlands Pharmacovigilance Centre Lareb and asked to participate. In addition assessors of ADRs employed by the Netherlands Pharmacovigilance Center Lareb, the Dutch Medicines Evaluation Board (MEB), and the pharmaceutical industry were asked to participate. Out of each group at least two persons were interviewed. Interviews were conducted until the interviews did not provide new information with respect to the research question.

The interview had five sections: 1) information about and work experiences of the participant, 2) familiarity with Lareb, 3) elements considered important concerning ADR reporting, 4) differences healthcare professional and patient reports, and 5) value of patient reports. The interviews were in Dutch and were performed by two researchers (LR and SW). Interviews were translated at the end of the analysis. All interviews were audiotaped and transcribed verbatim. Transcripts were validated by sending a summary of the interview to the participant [5]. Content analysis was used for data analysis. All transcripts were coded individually by two researchers (LR, SW) with the

support of QRS NVivo version 9.2.81.0., a software program for structuring qualitative data [6]. The Cohen's Kappa coefficient (κ) was calculated to measure the degree of agreement. We used the following standards for strength of agreement for the κ: 0.01-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial, and 0.81-1.0 = almost perfect [7]. Some elements that were typical examples of elements found important by patients or healthcare professionals were illustrated by quotes. For this study Ethics committee approval was not required, as Dutch legislation does not request this for studies which do not affect the patient's integrity. Participant data were sampled and stored in accordance with privacy regulations. Written informed consent was obtained from all participants prior to the interview [8].

RESULTS

In total 16 interviews were conducted; nine with reporters (three patients, two pharmacists, two general practitioners, two specialist doctors) and seven with assessors of adverse drug reactions. The κ showed substantial agreement in half of the transcripts and almost perfect agreement in the other half. Table 1 summarizes what elements of information about an ADR were considered important by reporters and assessors of ADRs.

Elements of information which were explicitly brought up during the interviews were the impact of the ADR on the patient's daily life and information regarding causality. The impact, often in combination with its severity, was mentioned by the patients. One patient who reported abdominal pain and a bloated belly associated with the use of pravastatin said: '*I could not keep this up anymore, I could not wear*

Table 1. *Elements of information about an ADR that were considered important by reporters and assessors of ADRs.*

Topic	Elements within a topic
Information about the ADR	ADR, start date, time to onset, treatment, seriousness[8], other aspects that could have caused the ADR, detailed description of ADR, de- and rechallenge, recurrence, recovery, recovery date, time to recovery, severity, impact of ADR on quality of life
Information about the drug	suspect drug, indication, RVG-code (Registration number for drugs), start and stop date, interactions, dosage, pharmaceutical form, actions after ADR, concomitant drugs, contra indication
Information about the patient	sex, date of birth, body weight, height, medical history, co morbidity, allergy, life style, familial diseases, compliance, metabolism, past drug therapy
Additional information	test results, letter of resignation, literature, incidence, confounding by indication, opinion of healthcare professional and patient, actions taken by patient, self-management patient

my clothes, not even my underwear, it was all too much for me' Another patient explained: *'It* (the ADR) *distracted from other things in life'.*

The impact was also mentioned by healthcare professionals. For example a pharmacist who explained the impact of an oily taste in one of his patients after the use of amlodipine: *'You are confronted with it the whole day, you cannot even enjoy your meal and it influences your ability to enjoy things'.* Information important for causality assessment was mentioned by all groups, however less explicit by patients. A general practitioner said: *'I look at other aspects of the patient such as concomitant medication, interactions, medical history. Also age, it is more likely a 70-year-old gets an ADR than a 20-year-old. This is also important information'.* Other elements of information considered important involving causality were for example the time course of the ADR, test results, and patient's medical history. In addition to the above, assessors of ADRs also found it important that the reported information is "correct". This is illustrated by the quote of one of the assessors: *'Yes, I think your first reaction is that you would say you would like as much information as possible. But, when I think about it, I would say I would like the information to be as specific as possible'.*

The impact of the ADR on the patient's daily life was mentioned less explicit in the interviews by assessors of ADRs. Assessors working at Lareb found that information about the impact can be very useful for the writing of a proper personalized feedback to the patient, since Lareb writes a personalized feedback to each reporter [1,9]. This aspect was not mentioned by assessors at the MEB or the pharmaceutical industry.

Patient reporting

Patient reporting was generally seen as a very positive development for pharmacovigilance. It was thought that patients could give a detailed description of the ADR because they are the one that actually experience the ADR. Some interviewees added that additional clinical information of a healthcare professional might be necessary for understanding certain ADRs.

Strengths and limitations

The number of participant involved in this study is limited but, because all parties involved in ADR reporting are included the authors believe that a clear overview is obtained of all elements of information that are considered important regarding ADR reporting.

CONCLUSION

This article gives an overview of views of reporters (patients and healthcare professionals) and assessors of ADRs on what they consider important information about a reported ADR. Patients reported the severity and impact of ADRs on their daily life to be important subjects. In the interviews with the healthcare professionals and assessors the focus was mainly on causality. The correctness of the given information is considered to be very important by ADR assessors. Regarding patient reporting the overall view was positive. Because healthcare professionals and patients have different views regarding ADR reporting, in daily practice it is important to receive reports of both groups in order to assess the true nature of the ADR.

The elements of information about ADRs found in this study will be used for a further quantitative comparison of patient and healthcare professional reports.

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2.2

Adverse drug reaction reports of patients and healthcare professionals – differences in reported information

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ABSTRACT

Objective: This study aims to explore the differences in reported information between adverse drug reaction (ADR) reports of patient and healthcare professionals and, in addition, to explore possible correlation between the reported elements of information.

Methods: This retrospective study compared the reported information between 200 ADR reports of patients and healthcare professionals. Reports were rendered anonymous and scored for the presence or absence of predefined elements of information. These elements can be objective (e.g. start date of the ADR) or subjective (e.g. the impact or severity of the ADR).

A two-sided Pearson's Chi-square test was used to detect statistically significant differences in the reported information. A Bonferroni correction was used to correct for multiple comparisons. Correlation between the elements of information was explored using categorical principal components analysis (CATPCA).

Results: Overall, healthcare professionals had a higher score for the presence of objective and patients for subjective elements of information. Elements that were statistically significant more often reported by patients are the impact of the ADR and the patient's weight and height. Healthcare professionals statistically significant more often reported the medical history and the route of administration of the drug. CATPCA showed four clusters of elements of information that have fair correlation.

Conclusions: This study demonstrates the differences in reported information between ADR reports of patients and healthcare professionals. Patient reports are more focused on patient related information and the impact of the reported ADRs, whereas reports from healthcare professionals provide more clinically related information.

INTRODUCTION

Detection of new adverse drug reactions (ADRs) after marketing is often based on clinical observations in daily practice. Spontaneous reporting of ADRs is one of the main methods of detection of post marketing drug safety issues [1]. Traditionally, reporting of possible ADRs was reserved for healthcare professionals. Patients of only a few countries were able to report their ADR directly to the competent authority, for example in the USA since 1969, Denmark and the Netherlands since 2003, the UK since 2005 and Sweden since 2008 [2]. This altered after changes in the European pharmacovigilance legislation, allowing patients of all European member states to report drug concerns directly [3].

Patient reporting in pharmacovigilance

Previous research demonstrated that patients may have a positive complementary contribution to that of healthcare professionals by identifying different drug-ADR associations [4]. Besides, patients may report different information compared to healthcare professionals, resulting in broader information of the ADR. Over time, several studies were conducted to explore differences in reported information between reports of patients and healthcare professionals [5-10]. These studies mainly focused on directly measurable differences e.g. the kind of ADR and seriousness of the ADR. Less attention has been paid to subjective differences, for example the extent to which clinical aspects has been reported or the impact of the ADR on the patient's daily life. A study by *Avery et al.* in the UK comparing patients' descriptions of their ADRs to healthcare professionals demonstrated that detailed information about the impact of the ADR on the patient's daily life was given by patients, but was comparatively rare in healthcare professional reports [6]. Information about subjective matters about the ADR can be useful in the understanding of the tolerability of ADRs [11] and provides insight into the perception of the ADR by the patient. Insight in similarities and differences between reports of patients and healthcare professionals, including objective as well as subjective elements of information, is helpful in order to clarify the potential value of direct patient reporting to pharmacovigilance.

Correlation between reported elements of information

When comparing reports of patients and healthcare professionals it is interesting to take into consideration a possible correlation in reported elements of information. When the severity of the ADR is reported, it may be expected that the reporter also gives information about the impact. The same applies for example for information about to the suspected drug e.g. dosage unit, pharmaceutical form or indication. To the best of our knowledge possible correlation in reported elements of information

has not been explored before. This study aims to explore the differences in reported information between ADR reports of patient and healthcare professionals and in addition to explore possible correlation between the reported elements of information.

METHOD

A retrospective study of 200 ADR reports from patients and healthcare professionals was performed which looked at similarities and differences in reported information and possible correlation between reported elements of information. Reports of patients were compared to those of healthcare professionals in general and to the individual groups on the basis of reported elements of information.

In the Netherlands patients and healthcare professionals can report by means of an electronic or paper reporting form. Almost 95% of all reports are done by means of the electronic form. The reporting form contains standardized questions of which some are mandatory in the electronic form. Besides, reporters can give additional information in a free text field. With exception of the question about medical history, which is only present on the healthcare professional reporting form, both reporting forms obtain the same information.

Study population

From 1 March 2012, the first 100 reports of patients and the first 100 reports of healthcare professionals (pharmacists, general practitioners and specialist doctors) were selected from the database of the Netherlands Pharmacovigilance Centre Lareb. For each reporter only one ADR report was included.

Rating of ADR reports

Reports were scored for the presence or absence of predefined elements of information. A list of elements of information was obtained from a previous study in our centre, exploring information that was found to be important regarding ADR reporting by reporters and assessors of ADRs [12]. Seriousness of the reports was scored according to the international CIOMS criteria [13].

All included reports were blinded by removing the type of source (either patient or healthcare professional). Reports were rendered anonymous and scored by one of five experienced ADR assessors (FH, IO, MH, PH, SK). ADR assessors are professionals which are trained to do a causality assessment of ADR reports. At Lareb these assessors are mainly medical doctors or (hospital)pharmacists. In assigning the reports none of the assessors received reports they had previously seen before. Prior to the study the assessors were trained to score the reports. After training the assessors

scored 10 reports individually. The degree of agreement in scoring was determined by calculation of the Fleiss Kappa coefficient (κ). Training was continued until substantial agreement (κ of 0.60) was achieved [14].

Statistical analysis

A Pearson's Chi-square (X^2)-test was used to study differences in the number of reported elements of information. Significance was based on a two-sided Pearson's X^2-test; $P<0.05$. To correct for multiple comparisons, a Bonferroni correction was conducted (corrected $\alpha = \alpha$/number of independent significance tests) [15]. It adjusted for 56 independent tests leading to the corrected p-value for significance of < 0.001.

Correlation testing of pharmacovigilance data can be performed using *categorical principal components analysis* (CATPCA). CATPCA is mostly used in social and behavioural sciences in order to reduce large numbers of variables to a small number of uncorrelated linear combinations that represent most of the information found in the original variables [16,17].

CATPCA based on two dimensions was conducted to investigate which elements of information possibly correlate. In CATPCA the VAF-score (variance accounted for) can be used to determine the degree of correlation. The following rules of thumb for VAF can be used: 10% is poor, 20% is fair, 30% is good, 40% is very good, and 50% is excellent [16]. For this study, elements with at least fair correlation were selected. Elements of information that were 100% reported were excluded from the CATPCA, since no differences between both study groups exist. Data were analysed using the statistical software program SPSS Statistics, version 20.0 (SPSS, Chicago, IL).

RESULTS

Differences in reported information

An overview of the number of elements of information reported by patients and healthcare professionals is shown in Table 1.

Six elements of information are statistically differently reported by patients and healthcare professionals. Patients more often reported the impact of the ADR (17% versus 2%) and patient's weight and height (respectively 94% versus 52% and 93% versus 54%). healthcare professionals more often reported the route of administration of the drug (92% versus 41%) and the medical history (61% versus 9%). Further, a statistically significant difference was seen for the seriousness of the ADR between reports of patients and specialist doctors (10% versus 42%).

Table 1. *Comparison of elements of information reported by patients and healthcare professionals*

Elements of information	% Patient reports	% Healthcare professional reports	X^2-test P value	% General practitioners^ (X^2-test P value)	% Pharmacists$^+$ (X^2-test P value)	% Specialist doctors^ (X^2-test P value)
Adverse drug reaction						
ADR**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
Start date of the ADR**	98	97	1.00$^{\neq}$	97 (1.00$^{\neq}$)	97 (0.75)	97 (1.00$^{\neq}$)
Time to onset	95	96	1.00$^{\neq}$	91 (1.00$^{\neq}$)	97 (0.62)	97 (1.00$^{\neq}$)
Outcome ADR**	91	81	0.04	85 (0.32$^{\neq}$)	68 (0.01)	91 (0.99$^{\neq}$)
Treatment of the ADR**	37	39	0.77	45 (0.34)	32 (0.63)	40 (0.81)
ADR occurred after use of a similar drug**	12	10	0.65	9 (0.76$^{\neq}$)	12 (1.00$^{\neq}$)	9 (0.76$^{\neq}$)
No ADR after use of a similar drug	7	1	0.07$^{\neq}$	3 (0.67$^{\neq}$)	0 (0.19$^{\neq}$)	0 (0.19$^{\neq}$)
Other aspects that could have caused the ADR**	15	14	0.84	12 (0.78$^{\neq}$)	12 (0.71$^{\neq}$)	18 (0.66)
Seriousness**	**10**	25	0.01	12 (0.75)	21 (0.14$^{\neq}$)	**42 (<0.001)**
Detailed description of the ADR	49	30	0.01	42 (0.51)	21 (0.01)	27 (0.03)
Course of the ADR	30	28	0.76	12 (0.04)	35 (0.57)	36 (0.50)
ADR after increase/decrease of dose, after withdrawal of drug	5	4	1.00*	0 (0.33$^{\neq}$)	3 (1.00)	9 (0.41$^{\neq}$)
Dechallenge	10	12	0.65	9 (1.00$^{\neq}$)	21 (0.14$^{\neq}$)	6 (0.73$^{\neq}$)
Rechallenge	9	3	0.07	3 (0.45$^{\neq}$)	3 (0.51$^{\neq}$)	3 (0.45$^{\neq}$)
Recurrence	5	5	1.00	9 (0.41$^{\neq}$)	0 (0.39$^{\neq}$)	6 (1.00$^{\neq}$)
Recovery date**	0	4	0.12$^{\neq}$	3 (0.25$^{\neq}$)	3 (0.25$^{\neq}$)	6 (0.06$^{\neq}$)
Time to recover	4	8	0.23	6 (0.64$^{\neq}$))	6 (0.64$^{\neq}$)	12 (0.11$^{\neq}$)
Impact of the ADR on the patient's daily life	**17**	**2**	**<0.001**	0 (0.07$^{\neq}$)	3 (0.29$^{\neq}$)	3 (0.29$^{\neq}$)
Severity of the ADR	30	12	0.01	12 (0.04)	12 (0.04)	12 (0.04)
Drug						
Suspect drug**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
RVG code*	27	19	0.18	6 (0.01)	47 (0.03)	3 (0.01)
Interaction*	2	3	1.00$^{\neq}$	3 (1.00)	9 (1.00$^{\neq}$)	3 (1.00$^{\neq}$)
Start date drug**	98	100	0.50$^{\neq}$	100 (1.00$^{\neq}$)	100 (1.00)	100 (1.00$^{\neq}$)
Stop date drug*	58	66	0.24	73 (0.13)	59 (0.9)	67 (0.38)
Drug dosage*	77	93	0.01	90 (0.08)	100 (0.01)	88 (0.18)
Dosage unit*	77	87	0.07	88 (0.18)	91 (0.18)	82 (0.56)
Route of administration*	**41**	**92**	**<0.001**	**90 (<0.001)**	**97 (<0.001)**	**88 (<0.001)**
Pharmaceutical form*	74	86	0.03	82 (0.37)	94 (0.013)	82 (0.36)
Indication*	86	89	0.52	90 (0.56)	79 (0.36)	97 (0.12$^{\neq}$)
Actions after occurrence of ADR	94	95	0.76	94 (0.99$^{\neq}$)	97 (0.49$^{\neq}$)	94 (0.99$^{\neq}$)
Other suspect drugs*	4	14	0.01	12 (0.11$^{\neq}$)	9 (0.37$^{\neq}$)	21 (0.01$^{\neq}$)
Concomitant drugs**	36	46	0.15	33 (0.78)	62 (0.01)	42 (0.51)

Table 1. *(continued)*

Elements of information	% Patient reports	% Healthcare professional reports	X^2-test P value	% General practitioners^ (X^2-test P value)	% Pharmacists+ (X^2-test P value)	% Specialist doctors^ (X^2-test P value)
Batch number	1	2	1.00#	6 (0.15#)	0 (1.00#)	0 (1.00#)
Contra indication	1	0	1.00#	0 (1.00#)	0 (1.00#)	0 (1.00#)
Extra information about the drug use	10	5	0.18	3 (0.29#)	9 (1.00#)	3 (0.29#)
Patient's characteristics						
Sex**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
Date of birth**	100	100	NA	100 (NA)	100 (NA)	100 (NA)
Patient's weight*	**94**	**52**	**<0.001**	**61 (<0.001)**	**24 (<0.001)**	**73 (<0.001)**
Patient's height*	**93**	**54**	**<0.001**	**52 (<0.001)**	**24 (<0.001)**	**61 (<0.001)**
Medical history/co morbidity/ allergy*	**9**	**61**	**<0.001**	**56 (<0.001)**	**47 (<0.001)**	**79 (<0.001)**
Past drug therapy	8	10	0.62	3 (0.45#)	15 (0.31#)	12 (0.49#)
Life style (occupation, diet, sports)	4	2	0.68#	0 (0.57#)	6 (0.64#)	0 (0.57#)
Compliance	0	1	1.00#	0 (NA)	3 (0.25#)	0 (NA)
Additional information						
Test results in relation with the ADR	8	10	0.62	6 (1.00#)	9 (1.00#)	15 (0.31)
Diagnosis confirmed with clinical test	2	8	0.05	3 (1.00#)	9 (0.10#)	12 (0.03#)
Discharge letter	1	2	1.00#	0 (1.00#)	0 (1.00#)	6 (0.15#)
Literature	2	4	0.68#	3 (1.00#)	6 (0.27#)	3 (1.00#)
Incidence	2	1	1.00#	0 (1.00#)	3 (1.00#)	0 (1.00#)
ADR present/absent in SPC	3	0	0.25#	0 (0.57#)	0 (0.57#)	0 (0.57#)
Confounding by indication	3	4	1.00#	0 (0.57#)	6 (0.60#)	6 (0.60#)
Information about specific groups of patients	5	3	0.72#	3 (1.00#)	3 (1.00#)	3 (1.00#)
ADR seen before by the reporter	6	1	0.12#	3 (0.68)	0 (0.34#)	0 (0.34#)
Opinion/clinical experience healthcare professional	14	13	0.84	12 (1.00#)	9 (0.56#)	18 (0.58#)
Patient's thoughts about causality	12	2	0.01	0 (0.04#)	4 (0.52#)	0 (0.04#)
Contact with or between healthcare professionals	23	10	0.01	9 (0.08)	4 (0.16)	9 (0.08)
Self-management patient	9	5	0.27	3 (0.26#)	12 (0.96#)	3 (0.26#)

* Standardized question on ADR reporting form

** Standardized and mandatory question on ADR reporting form

Fishers exact test

^ Total number healthcare professionals included is 33

+ Total number of healthcare professionals included is 34

NA: Data not applicable

Although not statistically significant, some elements showed a difference in reporting worth mentioning. The course and outcome of the ADR, a detailed description of what happened, the severity of the ADR, contact with or between healthcare professionals and patient's thoughts about causality were more often reported by patients compared to healthcare professionals. Elements related to the drug use: drug dosage, the pharmaceutical form of the drug, and other suspect medication were more often reported by healthcare professionals. Further, a diagnosis confirmed with clinical tests was more often reported by specialist doctors compared to patients. The registration number for drugs was more often reported by pharmacists followed by patients, which subsequently reported more often than general practitioners and specialist doctors.

Correlation between reported elements of information

Of all 56 elements included in this study, 52 were included in the CATPCA. In Table 2 the 20 elements with a VAF-score of ≥ 20% are shown. Roughly, a distinction can be made for 4 clusters of correlated elements as shown in Figure 1. The first clusters refers to patient related information; patient's weight and height. Elements of

Table 2. *Elements of information in CATPCA with VAF-score ≥20%.*

Number	Element of information	VAF score	Cluster
1	Patient's weight	0.48	A
2	Patient's height	0.47	A
3	Impact of the ADR on the patient's daily life	0.20	B
4	Patient's thoughts about causality	0.25	B
5	Detailed description of the ADR	0.23	B
6	Severity of the ADR	0.20	B
7	Contact with or between healthcare professionals	0.23	B
8	Opinion/clinical experience healthcare professional	0.27	C
9	Course of the ADR	0.33	C
10	Recurrence	0.20	C
11	Test results in relation with the ADR	0.26	C
12	Contra-indication	0.35	C
13	Past drug therapy	0.22	C
14	Time to recovery	0.31	C
15	Discharge letter	0.43	C
16	Pharmaceutical form	0.31	D
17	Route of administration	0.45	D
18	Drug dosage	0.20	D
19	Dosage unit	0.24	D
20	Start date of the ADR	0.24	-

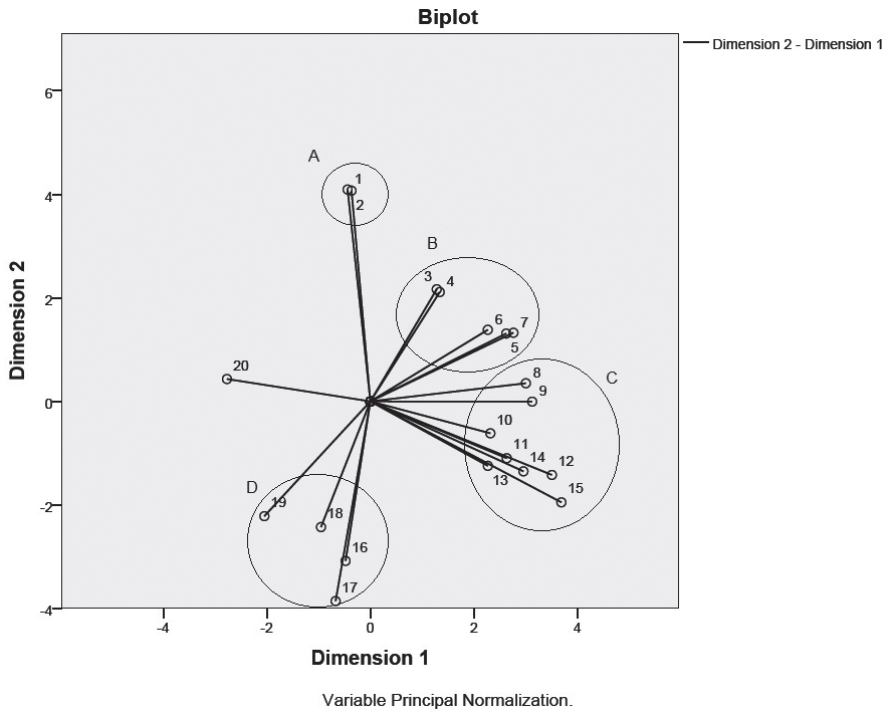

Figure 1. *Categorical principal components analysis*

this cluster (A) are statistically significant more often reported by patients. Elements in the second cluster (B) are mostly related to the patient's perception of the ADR, e.g. the impact and severity of the ADR. Although not all statistically significant, these elements are more often reported by patients. The third cluster (C) contains additional Information on the ADRs e.g. test results in relation with the ADR and past drug therapy. With the exception of the test results, there is no difference in reporting between patients and healthcare professionals for elements in cluster C. The final cluster (D) refers to drug related information; e.g. drug dosage and dosage unit. Although not all statistically significant, most of these elements are more often reported by healthcare professionals.

DISCUSSION

This study demonstrates the differences in information reported by patients and healthcare professionals. The Netherlands Pharmacovigilance Centre Lareb has long time experiences with patient reporting and previous studies learned that there are differences in reported information between both groups [6-10,18]. However, the

exact nature of the differences was not yet clarified. By including a large number of elements of information we aimed to give a comprehensive view of the differences in reported information between reports of patients and healthcare professionals. Besides, correlation between the included elements of information was explored to obtain a deeper insight in the nature of the reported information.

This study found differences in both objective and subjective elements of information. Healthcare professionals more often reported objective information compared to patients. Probably they might recognize the importance of these elements more or are more equipped to provide this information. It is remarkable that clinical information like test results were not more often reported by healthcare professionals. A general idea about reporting by healthcare professionals is that they report additional information to clinically support their ADR report. This idea was not supported by this study. Test results are reported, albeit minimal.

Distinguishing the different groups of healthcare professionals and comparing them to patients, only specialist doctors more often reported a diagnosis which was confirmed with test results. However, the reporting of addition information to clinically support the ADR might be associated with the specific drug-ADR associations, which was not included in this study design.

Elements more often reported by healthcare professionals were mainly standardized questions on the ADR reporting form, e.g. route of administration of the drug and the patient's medically history. Additionally, CATPCA showed one cluster of elements of information referring to drug related information, cluster D. Most of these elements are more often reported by healthcare professionals. The element *medically history*, which is more often reported by healthcare professionals, deserves special attention. This element is a standardized question on the healthcare professional reporting form but is not on the patient reporting form. The detected difference is therefore to be expected.

Subjective elements of information are mostly reported by patients. CATPCA showed one cluster of elements of information that are of subjective nature, cluster B about the perception of the ADRs. All elements of information in this cluster are more often reported by patients. Patients more often gave a detailed description about their perception of the ADR and the impact it had on their daily life. This kind of information was less frequently reported by healthcare professionals. Information about the severity and the impact of an ADR can be useful for the understanding of the tolerability of ADRs [19]. Medical seriousness according to the CIOMS criteria may differ from patients' views on what constitutes a serious problem [20]. Patients' information leaflets mostly lack this kind of information [21]. When such information is documented and made available, this can be helpful for patients in the acceptance and handling of their ADRs. Because this information is rarely reported by healthcare professionals, patients can give added value by reporting such elements of information.

Besides objective information patients more often report their weight and height compared to healthcare professionals. For patients this kind of information is a known fact while for healthcare professionals this information might not always be available.

Comparison to other studies

Only a few elements of information included in this study could be compared to literature. Differences in the reporting of serious ADRs has been explored in Denmark, the UK and the Netherlands [5,7,10]. Comparing reports of patients and healthcare professionals, no differences in seriousness of reported ADRs were found in Denmark and the Netherlands [5,7]. In the UK, healthcare professionals statistically significant more often report serious ADRs compared to patients [10]. In the Netherlands a statistically significant difference was only seen when comparing patients to specialist doctors [7]. As in the current study, other studies demonstrated that the impact of the ADR on the patient's daily life and a detailed description of the ADR are more often reported by patients [6,9,18].

Since the beginning of direct patient reporting to pharmacovigilance several studies were performed to explore their value to pharmacovigilance. A recent systematic review on patient versus healthcare professional reporting concluded that despite the large and increasing number of national pharmacovigilance schemes that accept patient reports, only a few comparitive studies have been undertaken of patient and healthcare professionals reporting. The true value of patient reports to pharmacovigilance will remain unknown unless more comparative evaluations are undertaken [8]. This current study contributes to clarify the potential value of direct patient reporting to pharmacovigilance. The differences found in this study indicate that reports of patients as well as healthcare professionals are needed in order to obtain a comprehensive view of the ADR.

Strengths and weakness

For this study a large set of elements of information was included to get a comprehensive view of the essential differences between information reported by patients and healthcare professionals. A strength of this study is that it took into account more information that only the mandatory fields in the reporting form. Also the additional information from the narrative of the reports and added information like attached lab-results, hospital discharge letters but also subjective elements like the impact of the ADR were compared. Further, a new aspect was introduced, namely the correlation between the reported elements of information. Because the reports had to be scored by trained assessors, a limited number of 200 reports, not matched on ADR, was selected at random. The reported information may depend on the drug-ADR association. e.g. for a report about hepatitis you would rather expect test results compared to

a report about severe withdrawal syndromes or taste disorders. For these reports you would rather expect information about the severity or impact. Further research on reported information for specific drug-ADR associations is needed.

From the results of this study no conclusions can be drawn about the clinically relevance of the reported information between both groups. The focus was to describe the nature of the reported information. A follow-up step will be to explore differences in causality between reports of patients and healthcare professionals. The primary aim of a spontaneous reporting system in pharmacovigilance is the timely detection of unknown ADRs. For this purpose, it is important to make a proper assessment of the drug-ADR association. Further research would be needed to determine whether the differences in reported elements of information between patients and healthcare professionals affect this causality assessment.

CONCLUSION

This study demonstrates the differences in reported information between ADR reports of patients and healthcare professionals. Patient reports are more focused on patient related information and the impact of the reported ADRs, whereas reports from healthcare professionals provide more clinically related information.

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2.3

The impact of experiencing adverse drug reactions on the patient's quality of life; a retrospective cross-sectional study in the Netherlands

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ABSTRACT

Introduction: There is little information as to what extent adverse drug reaction (ADRs) influence the patient's health related quality of life (HR-QOL). From a pharmacovigilance perspective, capturing and making the best use of this information remains a challenge. The Netherlands Pharmacovigilance Centre Lareb received about 1800 reports, of which more than 90% of patients, after the packaging of the drug Thyrax® (levothyroxine), Aspen Pharma Trading Limited, Ireland, changed from a brown glass bottle to a blister package in the Netherlands.

Objective: To explore the impact of ADRs on HR-QOL in patients who reported a possible ADR to Lareb in relation to the change of the package of the drug Thyrax® . A secondary objective was to explore factors correlated to change of HR-QOL.

Methods: Patients who reported an ADR in relation to the packaging change of Thyrax® were included. A web-based adapted version of the COOP/WONCA questionnaire was sent to explore the HR-QOL *before* versus *during* the ADR, expressed on a 5-point scale: no impact (1) to a high impact (5). Multivariable linear regression analysis was used to identify factors correlated to change in HR-QOL.

Results: overall 1,167 reporters returned the questionnaire (71.2% response rate). Difference in HR-QOL was -0.8 for physical, -1.2 for mental, -1.4 for daily activities, -1.3 for social and -1.3 for overall health status ($p<0.001$ for each domain). Age, sex, educational level of the patient and absence from work due to an ADR were correlated to at least one domain, while severity of the ADR was found to be correlated to all domains of HR-QOL.

Conclusion: Patients who reported possible ADRs after the packaging change of Thyrax® experienced a significant decrease in HR-QOL. This impact was the highest for the domains 'daily activities', 'overall health status' and 'mental health' and the lowest for 'physical fitness'.

INTRODUCTION

Adverse drug reactions (ADRs) can have a great impact on a patient's health related quality of life (HR-QOL), i.e. the perception of physical and mental health, the perceived need for health care and preferences about treatment and outcome [1]. Unfortunately within pharmacovigilance, for example as part of a spontaneous ADR reporting system, systematically gathering data on HR-QOL is still uncommon to do.

Information about the impact of ADRs on a patient's HR-QOL can be useful for several purposes. Firstly, it can be systematically used during the process of signal selection. Pharmacovigilance centres primary aim the timely detection of unknown ADRs or new information about known ADRs. This process is also known as 'signal detection'. In practice, a signal is a clinically important event that, if found to be drug related, might have impact on patient management or the balance of benefits and risks [2]. In the process of selecting which potential signals deserve attention, ADR reports that are classified as 'serious' according the CIOMS criteria often have priority over other reports. These criteria include reactions leading to (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events, congenital abnormalities and other medically significant reactions [3] Non-serious ADRs, e.g. headache, itchiness or muscle pain, can however have a great impact on patient's HR-QOL. Systematically gathering this information may help to identify subgroups of patients with relatively poor HR-QOL and can in this way be used for signal prioritization.

Secondly, for healthcare professionals, information about the impact of an ADR can give them insight how patients feel and how satisfied they are with the treatment [4]. This can be illustrated by a study of *Baiardini et al.*, exploring HR-QOL and well-being in patients with drug-induced anaphylactic shock [5]. That an anaphylactic shock has impact on the patients HR-QOL is to be expected. However, it was also found that most patients were worried to take any medication after the ADR occurred, even those drugs that did not cause the allergic reaction. Healthcare professionals can use information about the impact of ADRs to select the most appropriate treatment strategies for the individual patient and to provide appropriate information about these ADRs.

Finally, for patients information about the impact of ADRs can be useful in the process of understanding and accepting ADRs. *Lorimer et al.* explored patient's experiences of severe ADRs [6]. Aside from a direct physiological effect of ADRs on a patient, emotions such as disbelief, anger, fear, frustration and isolation were commonly expressed. *Guo et al.*, who studied ADRs in tuberculosis patients, showed that ADRs carry a higher mental well-being burden than a physical one [7]. *Van Hunsel et al.* demonstrated that next to altruistic motives, 'I wanted to be heard' is a trigger for

patients to report ADRs [8]. The contact between the patient and their HCPs may also influence how patients experience the impact of ADRs on their HR-QOL. Awareness of the possible impact of ADRs on HR-QOL may help patients in the understanding and accepting of their ADRs and give them greater perspective on the burden of their disease.

Given the relative lack of literature on how information about the impact of ADRs on patient's HR-QOL can be captured in spontaneous ADR reporting, research is needed. Since type and stage of a disease influences a patient's perception of the impact of an ADR, we considered it important to study a relatively homogenous group of patients. In the period from end of 2013 until summer 2015, the Netherlands Pharmacovigilance Centre Lareb received about 1800 reports after the packaging change of the drug Thyrax® (levothyroxine), Aspen Pharma Trading Limited, Ireland, [9]. This is a massive increase compared to the 167 reports received on levothyroxine in the period between 2006 and 2010 (average of 2-3 reports per month) [10]. Thyrax® was granted marketing authorization in the Netherlands on 6 June, 1980 and is indicated for the treatment of thyroid disorders [11]. End of 2013, the packaging changed from a bottle to a blister at the initiative of the Marketing Authorization Holder to improve protection against various environmental factors such as light, air, and humidity. According to the Marketing Authorization Holder the formulation of the product had not been changed. Additional studies indicated that tablets from both the bottle and the blister meet the quality requirements, however, tablets from the blister have a slightly better stability [12]. Despite these findings, Lareb received lots of reports. The most reported ADRs were symptoms of hyperthyroidism including palpitations, fatigue and headache, but symptoms of hypothyroidism were also reported as well as symptoms with no clear explanation. Most of the reports (85%) were submitted after media attention about the packaging change of Thyrax® in February 2015, see also Figure 1 [13]. Media attention consisted of national television and reporting in newspapers [14]. The reporting pattern for this specific drug after media attention resembled the reporting pattern in New Zealand after a formulation change for the drug Eltroxin® (thyroxine; GlaxoSmithKline, Germany) [15,16].

In the Netherlands patients have been able to report ADRs to the pharmacovigilance centre since 2003. The majority of the received 1800 reports on the packaging change were from patients (93%). All reports were assessed on a case-by-case by a trained pharmacovigilance assessor. A feedback was sent to all patients in response to their reported ADR [17,18]. On average, the ADRs were reported 33 (±20) weeks after the start date of the ADRs.

This study aims to explore the impact of ADRs on the HR-QOL of patients who reported to the Pharmacovigilance Centre Lareb a suspected ADR in relation to the packaging change of Thyrax®. We were also interested in factors that may influence

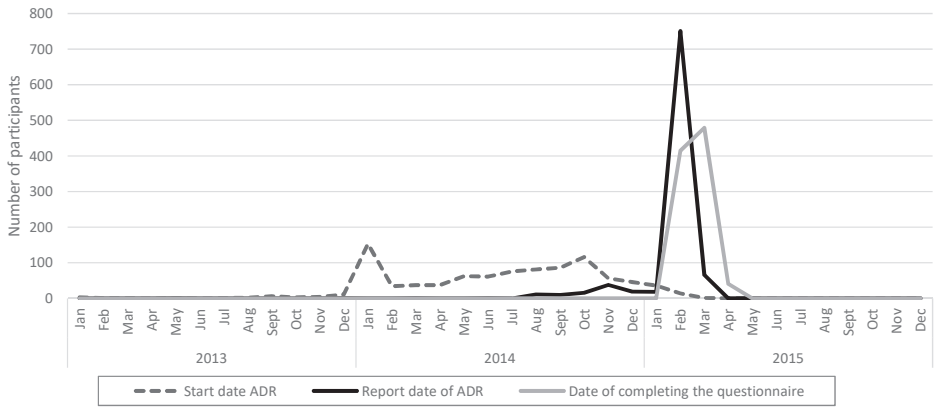

Figure 1. *Time lag between start date of the ADR, date of reporting and completing the questionnaire*

the change in HR-QOL, for example the outcome of the ADR or its severity. Therefore, the secondary aim is to explore factors correlated to change of HR-QOL during an ADR.

METHOD

Study population

The study population consisted of all patients who experienced an ADR after the packaging change of Thyrax® and reported this to the Netherlands Pharmacovigilance Centre Lareb until April 14, 2015.

Measurement of HR-QOL

In order to explore the impact of ADRs on the patient's HR-QOL an adapted version of the COOP/WONCA charts was used. This questionnaire was developed by the Dartmouth Primary Care Cooperative Research Network (COOP) and the World Organization of National colleges, Academics and Academic Associations of General Practitioners/Family Practitioners (WONCA). The Dutch version of the COOP/WONCA has been tested in a community setting and during a screening on hypertension. The validity and psychometric characteristics of the Dutch COOP/WONCA were found to be acceptable taken into account that it concerns a generic instrument [19]. The COOP/WONCA questionnaire is a self-reported, quick and simple questionnaire consisting of single-item scales to explore HR-QOL. The following domains of the COOP/WONCA were used: physical fitness, social activities, mental fitness, daily

activities and overall health status. The items were scored on a 5-level ordinal scale ranging from 1 (well for that domain) to 5 (poorly for that domain). HR-QOL was explored for the status at baseline (before the ADR) and during occurrence of the ADR. Subsequently a change score in HR-QOL was calculated.

Questionnaire development

A web-based questionnaire was designed and sent by e-mail using the Survey Monkey package [20]. On the first question sheet of the questionnaire we asked about the five domains of HR-QOL for the *situation at baseline*. On the subsequent sheet we asked about the HR-QOL *during* the ADR. Further, questions were posted about: recovery, seriousness and severity of the ADR, if the patient was absent from work due to the ADR, if the patient was able to discuss the ADRs in a satisfying matter with their healthcare professional and socio-demographic characteristics. Completing the questionnaire took approximately 5 to 10 minutes. For the questionnaire see Appendix 1.

Sending the questionnaire

An e-mail to invite participation in the questionnaire-study was sent to all eligible patients. A reminder was sent to all non-responders one week after the invitation. Collection of the responses finished two weeks after the first invitation was sent.

The invitational e-mail was uniquely linked to the questionnaire and the respondent's e-mail address. Therefore, the message could not be forwarded by respondents and only one response per e-mail address was allowed. Ethics committee approval was not required, as Dutch legislation does not request this for studies which do not affect the patient's integrity [21]. Participant data were sampled and stored in accordance with privacy regulations.

Data analysis

Overall HR-QOL and change score of HR-QOL were analysed for each domain using descriptive statistics. A paired sample t-test was used to analyse statistical significant differences in HR-QOL score before versus during the ADR. Multivariable linear regression analysis was carried out to explore factors correlated to changes in HR-QOL during an ADR. Potential correlating factors were the following items: recovery (yes/no), seriousness (yes/no) based on CIOMS criteria [3] and severity of the ADR (scale from 1 to 10), if the patient was absent from work due to the ADR (yes/no), if the patient was able to discuss their ADRs in a satisfying matter with their doctor and pharmacist (yes/no), age (≤20, 21-80 in six equally categories in steps of 10 years, > 80), sex and educational level (vocational school or lower/higher prof. education or higher). Backward selection procedure was used with a significance level of <0.05

to develop the model. To correct for multiple comparisons, a Bonferroni correction was conducted (corrected α = α/number of independent significance tests) [22]. It adjusted for 5 independent tests leading to the corrected p-value for significance of < 0.01. Data were analysed using IBM SPSS Statistics 22.

RESULTS

Overall

The questionnaire was sent to 1,638 patients and had a response of 71.2% (n=1167). The majority of respondents were female and between 41 and 60 years old (Table 1). The large majority of respondents had not recovered from the suspected ADR at the time of reporting. Only few reports were categorized as serious. More respondents reported they felt that they could discuss their ADRs better with their physician than with their pharmacist (Table 2).

The average severity of the suspected ADRs as experienced by patients was 6.7 on a scale from 1 (no severity) to 10 (high severity). The average time between occurrence of the ADRs and reporting was 8 months (SD 5 months). The average time

Table 1. *Respondents socio-demographic characteristics*

	N	%
Gender		
Female	1041	89.2
Male	121	10.4
Not reported	5	0.4
Age		
<20	14	1.2
21-30	41	3.5
31-40	104	8.9
41-50	273	23.4
51-60	377	32.3
61-70	262	22.5
71-80	54	4.6
>80	7	0.6
Not reported	35	3.0
Education		
Vocational school or lower	701	60.1
Higher prof. education or higher	455	39.0
Not reported	11	0.9

Table 2. *ADR related characteristics*

	N	%
Recovery ADR		
Yes	179	15.3
No	988	84.7
Serious ADRs		
Yes	40	3.4
No	1127	96.6
Absent from work due to the ADR		
Yes	569	48.8
No	304	26.0
Not reported/not applicable	294	25.2
Discuss the ADRs in a satisfying matter with their doctor		
Yes	809	69.3
No	185	15.9
Not reported/Not applicable	173	14.8
Discuss the ADRs in a satisfying matter with their pharmacist		
Yes	311	26.6
No	350	30.0
Not reported/Not applicable	506	43.4

between occurrence of the ADR and completing the questionnaire was 9 months (SD 5 months). See also Figure 1.

Quality of life scores

The overall HR-QOL at baseline, ranged from 1.7 to 2.7 (Table 3). In general, patients had the perception that their HR-QOL was good at baseline. There was a statistically significant decrease in HR-QOL scores for all domains, scores between -0.8 to -1.4 ($p<0.001$). The highest decrease was observed for the domains 'daily activities' followed by 'social activities' and 'overall health status'.

Table 3. *Health related quality of life for the domains: physical, social, mental, daily activities and overall health status*

Domain QOL	Before ADR	During ADR	Difference in QOL (SE)
Physical fitness	2.3	3.1	-0.8 (1.2)
Social activities	1.7	2.9	-1.3 (1.4)*
Mental fitness	1.8	3.1	-1.2 (1.3)*
Daily activities	1.7	3.1	-1.4 (1.2)
Overall health status	2.7	4.0	-1.3 (1.0)

* Difference due to rounding of results

Items correlated to change in HR-QOL

Multivariable linear regression analysis demonstrated several items that showed correlation to changes in HR-QOL (Table 4). The way the patients experienced the severity of the ADR was found to be correlated to all domains of HR-QOL. The higher the severity, the higher the impact on the patient's HR-QOL. Figure 2 shows the results on how patients experienced the severity of the ADRs. Sex was found to be correlated to the domains 'social activities' and 'mental fitness'. For female respondents the ADRs had a higher impact on HR-QOL for these domains. For age it was found that a higher age resulted in a higher impact of the ADR on HR-QOL for the domain 'physical fitness'. Educational level was found to be correlated to the 'physical' domain. An educational level of maximal vocational school resulted in a higher impact on HR-

Table 4. *Determinants in change of quality of life score*

Domain QoL	Constant	Correlated items	ß	95% CI	R^2
Physical	0.006	Severity	-0.18	-0.21; -0.15	0.112
		Age	0.06	0.02; 0.10	
		Education	0.22	0.10; 0.35	
Social	0.634	Severity	-0.29	-0.33; -0.26	0.188
		Gender	0.31	0.08; 0.54	
Mental	0.096	Severity	-0.24	-0.27; -0.20	0.140
		Gender	0.37	0.14; 0.60	
Daily activities	0.512	Severity	-0.28	-0.32; -0.25	0.201
Overall health status	0.107	Severity	-0.21	-0.24; -0.19	0.190
		Absent from work due to the ADR	0.003	0.002;0.004	

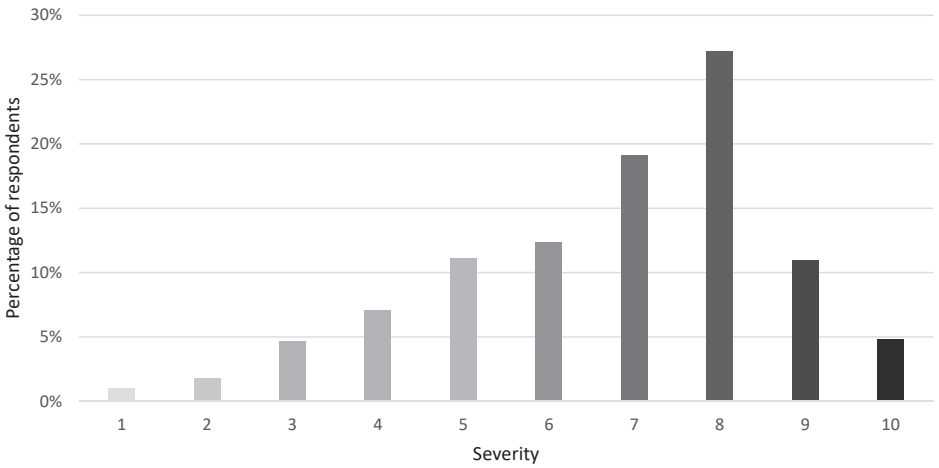

Figure 2. *Severity of the experienced adverse drug reactions*
Severity of the adverse drug reaction on a scale from 1 (no severity) to 10 (high severity) as experienced by patients

QOL compared to an education of higher prof. education/academic. Analysis further demonstrated that when patients were absent from work due to the ADR, this had a positive influence on the domain 'overall health status'.

DISCUSSION

In this study, we investigated with a questionnaire the impact of ADRs on HR-QOL of patients who reported a possible ADR to Pharmacovigilance Centre Lareb in association with a package change of the drug Thyrax®. Patients are increasingly systematically involved in the process of drug safety, going from drug development to pharmacovigilance [23]. Patients have been able to report ADRs directly in a growing number of countries. For pharmacovigilance centres it remains a challenge to capture some of the unique features of patient reports, like information on HR-QOL, and to make best use of this information in a spontaneous reporting system. Since the patient is the one who actually experienced the ADR, we believe that it is best to ask them about the impact it has on their HR-QOL. In spontaneous reports, information on the impact of the ADR on daily life is more present in patient than in healthcare professional reports [24,25]. This study demonstrated that the reported ADRs had a significant impact on the patient's HR-QOL. We found the highest impact on HR-QOL for the domains 'daily activities', 'overall health status' and 'mental health' and the lowest for 'physical fitness'. The decrease in HR-QOL ranged from -0.8 to -1.4, meaning that on average patient's HR-QOL dropped by one category on the 5-level ordinal scale. Interpreting the meaning of this change in HR-QOL, different perspectives have to be considered. From the point of view of the patient, a meaningful change in HR-QOL may be one that results in a considerable increase in complaints. When the patient is unable to carry out daily businesses, a change of one category on the 5-level ordinal scale may be a meaningful change in HR-QOL. In contrast, a meaningful change for the healthcare professional may be one that indicates a change in the therapeutic treatment or in the prognosis of the disease [26].

Items correlated to change in HR-QOL found in this study were age, sex and educational level of the patient, the severity, of the ADR, and absence from work due to the ADR. Little research has been done on the perceived severity of the ADRs in relation to HR-QOL. In our study, we measured severity as a subjective representation of how patients experienced the ADRs scored on a scale from 1 (no severity) to 10 (high severity). It was found to be correlated to all domains in HR-QOL. Studying HR-QOL in children with epilepsy, *Wu et al*. found that patients suffering from several different ADRs experienced lower HR-QOL [27]. Although they did not report the severity of the ADRs, experiencing several ADRs may theoretically be related to this.

It is important to note the difference between severity and the medical 'seriousness'. In our study, we used CIOMS criteria to assess the seriousness of an ADR report [3]. Other studies used different criteria. For example *Guo et al.* used the term 'major ADRs', defined as ADRs requiring hospital admission, additional treatment or discontinuation of tuberculosis medication which could be interpreted as 'serious ADRs' [7]. *Guo et al.*, using the Short-Form 36 questionnaire to measure HR-QOL, found that major ADRs influenced the physical, vitality and mental health domains. But because of the disparities in terminology, it is difficult to compare the results.

Education level was found to be correlated to 'physical fitness'. A higher educational level resulted in a lower impact on this domain. This result is supported by a study of *Davis et al.* exploring the extent to which treatment related ADRs were associated with cancer-specific and general QoL [28]. Exploring the relationship between drug related problems and HR-QOL in ambulatory, community-dwelling patients with musculoskeletal disorders, *Ernst et al.* found that the level of education was positively related with the change of the mental component and not to the physical [29]. In their study, *Ernst et al.* also explored the impact of 'positively addressing' drug-related problems since this can be an important step in improving HR-QOL. This determinant can be compared to 'was the patient able to discuss the ADRs in a satisfying matter with their healthcare professional' as used in our study. The present study as well as the study of *Ernst et al.* found no statistical significant effect for this item. Somewhat surprisingly, we found that 'absence from work due to the ADR' had a positive influence on the domain 'overall health status'. An explanation could be that patients who are still working despite the ADR experience much more discomfort compared to those who stay at home.

HR-QOL is a psychological construct and thus an abstract concept that is not directly observable. There is no gold standard to compare against, the standardized QoL questionnaires are the best instruments that are available [30]. There are several general HR-QOL questionnaires available, but none of them was specifically developed for the pharmacovigilance setting [31]. We chose the COOP/WONCA questionnaire, because it is a quick and simple, self-reporting tool which was found to be workable in this setting. In this questionnaire each question is a single-item measurement of an aspect of functional status and it is advised not to further aggregate the item scores into one index [19]. HR-QOL was studied using patients who reported to the pharmacovigilance centre. Several previous studies showed that patients consider the impact of an ADR on their HR-QOL an important subject and report about it more often compared to healthcare profesisonals [13,24,25,32,33]. This may partly explain our high response rate of 71.2%. Furthermore, the response rate may be high due to the media attention concerning the Thyrax® packaging problem. Finally, in general, previous studies with patient questionnaires also showed that patients are willing to provide extra information [8,34].

A strength of this study is that we included a relatively homogeneous study population of patients with a (chronic) thyroid disorder with the majority of patients being stable on their medication before occurrence of the ADRs [13]. Our population reported a relatively high HR-QOL at baseline, but slightly lower than a population (n=149, mean age 43.4 years, 47% female) studied by *Van Weel et al.* in Emmen, a rural town in the North of the Netherlands, using the COOP/WONCA questionnaire [19]. HR-QOL at baseline was the same for the domain 'social activities', but slightly worse in other domains: physical fitness (2.3 versus 1.8), mental fitness (1.8 versus 1.5), daily activities (1.7 versus 1.5) and overall health (2.7 versus 2.4). More research is needed in other patient groups with higher/lower HR-QOL at baseline.

Our study has several limitations. We used spontaneous reports to the Netherlands Pharmacovigilance Centre Lareb as a basis. One limitation is the period of time between onset of the ADR and the moment of reporting. If patients did not remember exactly how they felt before or during the ADR it may affect the accuracy of their recall regarding the impact of the ADRs on their HR-QOL. Another consequence of measuring the impact of ADRs on the patient's HR-QOL using data of a pharmacovigilance centre is that only those patients will be included who consider the ADRs important enough to report. A control group of patients who experienced ADRs but did not report to the pharmacovigilance centre is not available. Patients that do not report an ADR may experience a different change in HR-QOL as compared to those who did report it. Furthermore, we did not include the type of reported ADR into our analysis as a possible determinant. Since most patients reported several ADRs (average of 4 ADRs per report [9]), this was not considered feasible.

Practical implications

The perceived severity of the ADR was found to be a determinant for all domains of HR-QOL. The strong relationship between severity and impact is a valuable finding from the perspective of a pharmacovigilance centre. Adding HR-QOL questions to the regular ADR reporting form carries the risk that the form becomes too time consuming to complete. If one question about the severity gives a reflection of the patient's perception of the impact of the ADRs on their HR-QOL, this question could be used on the reporting form. This aspect should be further investigated. Information about the severity can be used in the process of signal selection and prioritization. When an ADR has a high severity in a significant share of the reports this may be a trigger to undertake action. As already highlighted, information about the impact of ADRs can also be valuable for other stakeholders in pharmacovigilance, for example healthcare professionals and patients. Follow-up studies are needed to explore in which ways this information can best be provided and used for these stakeholders.

In order to avoid one of the main limitations of our study, namely the recall bias, follow-up studies could focus on a prospective cohort approach, for instance the Lareb Intensive Monitoring system. In this system, patients receive a questionnaire directly after start of a new drug, followed by some follow-up questionnaires [35]. Using this method, you are able to ask patients about their HR-QOL directly after the event occurred.

CONCLUSION

Patients who reported possible ADRs after the packaging change of Thyrax® experienced a significant decrease in HR-QOL. This impact on HR-QOL was the highest for the domains 'daily activities', 'overall health status' and 'mental health' and the lowest for 'physical fitness'. Only the severity of the ADR was found to be correlated to all domains of HR-QOL.

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APPENDIX 1. QUESTIONNAIRE

General questions

1. Overall: age, gender and education of the participant.
2. Did the adverse drug reactions lead to any of the following? (prolongation of) hospitalization, life-threatening events reactions leading to death, disabling events or congenital abnormalities.*
3. What was the severity of the adverse drug reactions, on a scale from 1 (low severity) to 10 (high severity)?
4. Are the adverse drug reactions recovered?*
5. Were you absent from work due to the adverse drug reactions?*
6. Did you felt take seriously by your doctor when discussing the adverse drug reactions?*
7. Did you felt take seriously by your pharmacist when discussing the adverse drug reactions?*

**Questions were answered by 'yes', 'no' or 'not applicable'.*

Questions about the impact of the adverse drug reactions on the patient's quality of life

A. What was the hardest physical activity you could do for at least 2 minutes?
   1. Very heavy, (for example) run, at a fast pace
   2. Heavy, (for example) jog, at a slow pace
   3. Moderate, (for example) walk, at a fast pace
   4. Light, (for example), walk at a medium pace
   5. Very light, (for example) walk, at a slow pace or not able to walk

B. How much have you been bothered by emotional problems such as feeling anxious, depressed, irritable or downhearted and sad?
   1. Not at all
   2. Slightly
   3. Moderately
   4. Quite a bit
   5. Extremely

C. How much difficulty have you had doing your usual activities or tasks, both inside and outside the house because of your physical and emotional health?
   1. No difficulty at al
   2. A little bit of difficulty

3. Some difficulty
4. Much difficulty
5. Could not do

D. Has you physical and emotional health limited your social activities with family, friends, neighbors or groups?
   1. Not at all
   2. Slightly
   3. Moderately
   4. Quite a bit
   5. Extremely

E. How would you rate your health in general?
   1. Excellent
   2. Very good
   3. Good
   4. Fair
   5. Poor

3

Quality of clinical information in patient ADR reports

3.1

The quality of clinical information in adverse drug reaction reports by patients and healthcare professionals; a retrospective comparative analysis

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ABSTRACT

Introduction: Clinical information is needed to assess the causal relationship between a drug and an adverse drug reaction (ADR) in a reliable way. Little is known about the level of relevant clinical information about the ADRs reported by patients.
Objective: The aim was to determine to what extent patients report relevant clinical information about an ADR compared to their healthcare professional.
Methods: A retrospective analysis of all ADR reports on the same case, i.e. cases with a report from both, the patient and the patient's healthcare professional, selected from the database of the Netherlands Pharmacovigilance Center Lareb. The extent to which relevant clinical information was reported was assessed by trained pharmacovigilance assessors, using a structured tool. The following four domains were assessed: ADR, chronology, suspected drug and patient characteristics. For each domain, the proportion of reported information in relation to information deemed relevant was calculated. An average score of all relevant domains was determined, categorized as: poorly (≤ 45%), moderately (from 46- 74%) and well (≥ 75%) documented. Data were analysed using a paired sample t-test and Wilcoxon signed rank test.
Results: A total of 197 cases were included. In 107 cases (54.3%), patients and healthcare professionals reported a similar level of clinical information. Statistical analysis demonstrated no overall differences between both groups ($p = 0.126$).
Conclusions: In a unique study of cases of ADRs reported by patients and healthcare professionals we found that patients report clinical information at a similar level as their healthcare professional. For an optimal pharmacovigilance both healthcare professionals and patients should be encouraged to report.

INTRODUCTION

Pharmacovigilance is the science about 'the detection, assessment, understanding and prevention of adverse effects or any other drug related problems' [1]. Due to the design of pre-marketing clinical trials, i.e. small and homogeneous populations monitored for short periods of time, not all possible adverse drug reactions (ADRs) are detected. Additional ADRs, some of them serious, may be identified once a drug is used more widely and under more diverse conditions, e.g. concurrent use with other drugs or problems in using drugs by patients [2].

Pharmacovigilance centres maintain the national spontaneous reporting systems. Spontaneous reports of possible ADRs are a valuable source of information, e.g. in the USA spontaneous reports were the primary evidence source of drug safety issues resulting in drug safety communication from 2007 to 2009 [3]. Traditionally, reporting of possible ADRs was reserved for healthcare professionals. Only few countries allowed patients to report their ADRs directly, for example Australia since 1964 and the USA since 1969 [4]. Over the years, patient participation has increasingly been recognized as an important addition to pharmacovigilance [5,6]. Studies demonstrated that they contributed to identifying new ADRs as well as new information about known ADRs [7-9]. More and more countries started to accept ADR reports directly from patients, for example the Netherlands in 2003, the UK in 2005 and Sweden in 2008 [4]. Since 2012, changes in the European pharmacovigilance legislation made it possible for patients of all European Union member states to report drug concerns directly to the national pharmacovigilance centres [5].

A recent review showed that patient reporting adds new information and perspectives about ADRs in a way otherwise unavailable, for example information about the impact of ADRs on the patient's daily life. It also identified gaps in knowledge that should be addressed to improve our understanding of the full potential and drawbacks of patient reporting [10]. One of these aspects is the quality of clinical information. To assess the causal relationship between exposure to a drug and an ADR in a reliable way, clinical information is needed [11]. Studies which compared information reported by patients and healthcare professionals so far, focused on the completeness of information [12-24]. When it comes to causality assessment, an additional often ignored point of attention is the relevance of the clinical information provided. When a report lacks essential clinical information this makes it difficult to assess the reported data. In contrast, a brief report can still provide sufficient clinical information if all relevant information has been reported for that specific case.

As far as we are aware, it has not been studied to what extent patients report relevant clinical information compared to health professionals, in particular clinically relevant information needed to make causal assessments. The study aims to

determine to what extent patients report relevant clinical information about an ADR compared to their healthcare professional.

METHOD

Study setting and design

We used the database of the Netherlands Pharmacovigilance Center Lareb. Both patients and healthcare professionals are able to report possible drug concerns directly to Lareb by means of an electronic or paper reporting form. These forms contain standardized questions of which some are mandatory in the electronic form. Besides, reporters can give additional information in a free text field. Both reporting forms obtain the same information, with exception of a question about medical history, which is only present on the healthcare professionals reporting form. Reports from patients and healthcare professionals are handled in the same way for the cases-by-cases analysis, follow-up actions and signal detection.

The number of reports to the Netherlands Pharmacovigilance Centre Lareb continues to grow. In 2015, Lareb received about 8000 reports directly from patients and 6600 from healthcare professionals [25]. In the majority of cases, the ADR is either reported by the patient or the healthcare professional. Rarely, the patient and the patient's healthcare professional send reports independently on the same case. For this study, we conducted a retrospective analysis of all reports on the same case, i.e. reported by the patient and the patient's healthcare professional. This provided us the unique situation to directly compare the differences in clinical information reported by both groups.

Cases were identified as follows: all incoming reports were assessed case-by-case by a trained pharmacovigilance assessor. During this assessment the reports were automatically screened for other reports on the same case by checking the reported ADR (based on the Medical Dictionary for Regulatory Activities *MedDRA*® Higher Level Term coding) [26], suspected drug, patient's date of birth and gender, and time frame of maximal one year between both reporting dates. Using these data, the pharmacovigilance assessor determined if the reports were on the same case and labelled them accordingly in the database. The reports with the most comprehensive information will be included in database statistics, the other reports will not. Furthermore, the master report can be enriched with important clinical information that is only present in the slave report, for example concomitant medication.

Study population

All cases of reports that were made on the same case in the period April 1st, 2003 until October 1st, 2015 were selected from the Lareb database. When a case had more than two reporters, e.g. one patient report and two healthcare professional reports, the case was included twice: patient vs. healthcare professionals-1 and patient vs. healthcare professional-2. Exclusion criteria were: all cases that did not include a patient report or no healthcare professional report and cases that were received through pharmaceutical companies, since these were not directly sent to Lareb, e.g. other reporting forms may be used.

Outcomes

Our primary outcome was a comparison of the level of reporting clinical information between patients and healthcare professionals. This was determined using a Clinical Documentation tool (ClinDoc) [27]. This tool was recently developed and tested by Lareb as part of the WEB-RADR project, work package 4 [28]. It provides a structured approach to assess the level that relevant clinical data has been reported. Four domains were assessed: 1) description of the ADR, 2) chronology of the ADR, 3) suspected drug, and 4) patient characteristics. Each domain consisted of several subdomains (Table 1). To use this tool, first, the assessor indicated which subdomains were relevant in order to assess the report. Subsequently, the assessor indicated if this relevant information was present or absent. A score was calculated for each domain by dividing the number of subdomains with information present by the number of subdomains deemed relevant. The final score was the sum of the domain scores of all domains deemed relevant. The final score was categorized into one of three categories: well (≥75%), moderately (46-74%) or poorly (≤45%) documented.

As a secondary outcome we explored if proportions of information present in relation to the information deemed relevant was different for the individual (sub) domains. Because differences in the level of reporting for serious versus non-serious cases may be expected we did a sub-analysis for (non)serious cases. Seriousness was assessed according to Council for International Organizations of Medical Sciences (CIOMS) criteria which includes: ADRs leading to (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events or congenital abnormalities or other events considered serious by medical judgement [29].

All included reports were scored by two pharmacovigilance assessors independently. All reports were reformatted so that the assessors were kept blind whether reports originated from a patient or a healthcare professional. In total, six experienced pharmacovigilance assessors were involved. Reports about the same case, i.e. the report of the patient and the one of the healthcare professional, were scored by the same assessors but were presented to them at random. Differences between scores

Table 1. *The Clinical Documentation tool*

1	**ADVERSE DRUG REACTION (ADR)**	**Relevant? yes, no**	**Present? yes, no**
a	Proper description of the ADR		
b	Specification reaction 'localization' and 'characterization'		
	To strengthen the diagnosis (subdomain c or d or e applicable):		
c	Treatment; *or*		
d	Visual material (photo, video); *or*		
e	Lab values, test		

2	**CHRONOLOGY**	**Relevant? yes, no**	**Present? yes, no**
a	Latency (time to onset of ADR)		
b	Description of the course of the ADR		
c	Action taken on drug (e.g. drug withdrawn, increase of dose)		
d	Outcome of the ADR (e.g. recovered, not recovered)		

3	**SUSPECTED DRUG**	**Relevant? yes, no**	**Present? yes, no**
a	Brand name in case of drug substitution?		
b	Different forms or route of administration for suspected drug?		
c	Dose-relationship with ADR?		
d	Batch number of relevance?		

4	**PATIENT CHARACTERISTICS**	**Relevant? yes, no**	**Present? yes, no**
a	Risk factors/medical history/comorbidity/indication		
b	Concomitant medication		
c	Age/gender/length/weight		
d	Patient's life style or other risk factors		

for each domain were discussed until consensus was reached. Prior to scoring, all assessors were trained how to use the ClinDoc tool by means of scoring and discussing 15 reports.

Statistical analysis

General characteristics of the included cases were explored using descriptive statistics. We used a paired sample t-test for normally distributed data and a Wilcoxon signed rank test for non-parametric testing. Data normality was tested graphically using a histogram and numerically using Shapiro-Wilk test and a test for skewness. Statistical significance was based on $p<0.05$. Data were analyzed using the statistical software program SPSS Statistics, version 22.0 (SPSS, Chicago, IL).

RESULTS

General information sample characteristics

We included 197 cases with a report of the patient as well as the patient's healthcare professional. There was one case reported by the patient and two healthcare professionals. All the other cases contained one patient and one healthcare professional report. A report may contain several ADRs. In total, 227 ADRs were reported by both reporters, with most ADRs belonging to the System Organ Classes 'Nervous system disorders', 'Psychiatric disorders' , 'Gastrointestinal disorders' and 'Skin and subcutaneous tissue disorders'. Of the reported cases, 66 (33.5%) were classified as serious, according to CIOMS criteria [29]. Two examples of the description of information by patients and healthcare professionals are demonstrated in Table 2.

For all reports, assessors had agreement on the level of clinical information for an average of 8 reports (range 6 – 11). For cases where assessors had a difference score, the level of clinical information mostly differed by one category. Only two assessors had one report for which the score differed by two categories. Differences between scores for each domain were discussed until consensus was reached.

Table 2. *Summaries of two examples to demonstrate the differences and similarities in reporting*

Example	Patient	Healthcare professional
1	Male aged 40 years with rhabdomyolysis, creatine kinase >10.000 two weeks after start of paroxetine 20 mg, twice a day. The patient was hospitalized. The drug paroxetine was withdrawn; the patient has not recovered. Concomitant medication was reported, including start dates. Furthermore, it was reported that the patient is severe ill, could barely walk and has pain everywhere.	Male aged 40 years with rhabdomyolysis six weeks after start of paroxetine for depression. The patient was hospitalized. The drug paroxetine was withdrawn, and the patient was treated with an unknown infusion. The rhabdomyolysis recovered. The patient is of Moroccan origin. Kidney function was normal. Furthermore, no other laboratory abnormalities.
2	Female aged 71 years with a definitive loss of taste and smell one month after start of lisinopril 5 mg for high blood pressure. The drug lisinopril was withdrawn; the patient had not recovered. The loss of taste and smell suddenly started from one day to the other. The patient was examined by a neurologist, but he could not help her. When she ate, she felt like she was chewing on paper. Due to this, she lost body weight. Concomitant medication was reported, including the comment that she used this drug for years without any problems. Furthermore was reported that these complaints are a very serious handicap, especially for an elderly patient.	Female aged 71 years with anosmia and loss of taste one month after start of lisinopril for hypertension. The drug lisinopril was withdrawn. The patient had only slightly recovered. There were no other possible causes for the anosmia and loss of taste. Concomitant medication and patient's medical history were not reported.

Overall reporting of clinical information

Of all cases, for 107 (54.3%) cases the patient and the healthcare professional reported the clinical information on the same level. If the level was different, in most cases (87.8%), reports differed by only one category (well vs. moderately or moderately vs. poorly) and rarely (12.2%) by two categories (well vs. poorly). For 34 (17.3%) cases the patient scored one category higher compared to their healthcare professional. For four (2.0%) cases the patient scored two categories higher. For 45 (22.8%) cases the healthcare professional scored one category higher compared to the patient, for seven (3.6%) the healthcare professional scored two categories higher (Table 3a). Wilcoxon signed rank test demonstrated no statistically significant difference in category between both groups (p=0.126). Similar results were obtained when analysing serious and non-serious cases separately (respectively p=0.196 and p=0.356). For serious reports, 29 (43.9%) reports of patient and healthcare professional on the same case were classified in the same category. For non-serious reports this number was 78 (59.5%) (Table 3b-c).

Table 3a-c. *Level of reporting of clinical information patients vs. healthcare professionals, paired analysis*

	Healthcare professional			
	Well	Moderate	Poor	Total
(a) All reports				
Patient				
Well	72	31	4	107
Moderate	45	33	3	81
Poor	7	0	2	9
Total	124	64	9	197
(b) Serious reports				
Patient				
Well	20	12	1	33
Moderate	19	9	2	30
Poor	3	0	0	3
Total	42	21	3	66
(c) Non-serious reports				
Patient				
Well	52	19	3	74
Moderate	26	24	1	51
Poor	4	0	2	6
Total	82	43	6	131

Differences in domains scores

For the domains 'ADR', 'chronology' and 'suspected drug', patients and healthcare professionals scored in about 40% of cases similarly (i.e. scores differ less than 10%) (Figure 1). Healthcare professionals had higher scores for the domain 'patient characteristics' and probably therefore also had more often higher final scores. It has to be noted that the domain 'drug' was found to be relevant in only 13 (6.6%) cases.

Paired sample t-test and Wilcoxon signed rank test showed that healthcare professionals had a statistically significantly higher score for the domains 'patient characteristics' and again probably therefore a higher final score. The mean difference of the percentage score for these domains was however found to be small, 65.7% versus 57.1% (p=0.003) for 'patient characteristics' and 77.9% versus 74.7% (p=0.04) for 'final score'.

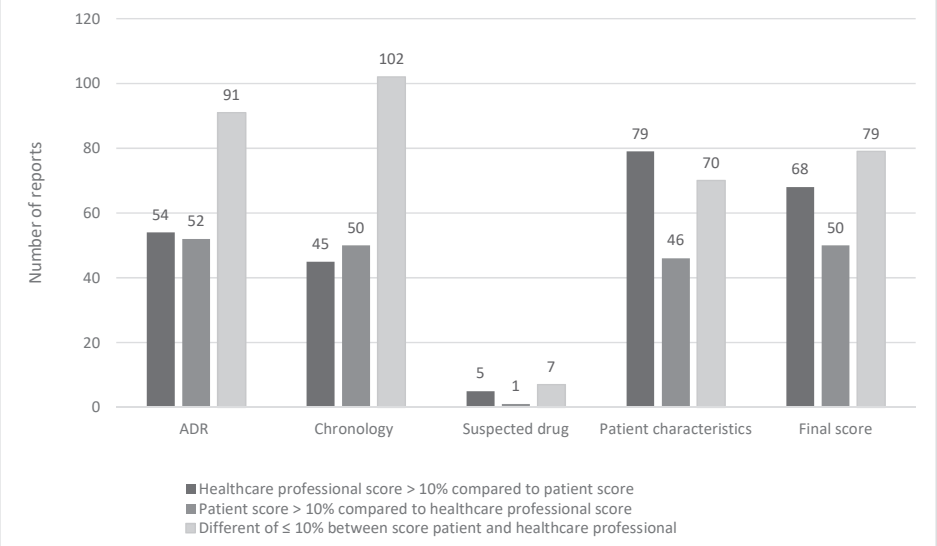

Figure 1. *Number of reports with similar and deviating scores, per domain for patients and healthcare professionals*

When the same analysis was performed using only the serious cases, healthcare professionals had a statistically significant higher score for the domains 'ADR' and 'patient characteristics'. The mean difference for the domain 'ADR' was small, 84.2% versus 75.6% (p=0.02). For the domain 'patient characteristics' the mean difference was 66.1% versus 55.5% (p=0.04). When the analysis was performed using only the non-serious cases, healthcare professionals had a statistically significant higher score for the domain 'patient characteristics'. The mean difference was however small, 58.1% versus 65.3% (p=0.03).

Differences in subdomain scores

For the subdomains, the 'concomitant medication' (a subdomain of the domain 'suspected drug') was statistically significant more often reported by healthcare professionals than patients (75% vs. 63.5%, p=0.017). For the other subdomains no statistical significant differences were found.

Remarkable findings were that 'visual material', 'lab values, tests' and 'patient's life style and other risk factors' were infrequently documented by both groups. In cases where these subdomains were considered to be relevant, respectively 19%, 25% and 20% of the patient reports and 20%, 39% and 25% of the healthcare professional reports contained information.

DISCUSSION

Healthcare professionals and patients reported clinical information about the ADR on a comparable level for over half of the cases. For only one third of all cases, the patient had a lower score compared to their healthcare professional. Vice versa, patients had higher scores for almost one fifth of the reports. Rarely, we found large differences in the level of reporting relevant information. Items included in the clinical documentation tool reflect items that are important for causality assessment. The results found in this study indicate that reports from patients are comparable to those of healthcare professionals when it comes to making a proper causality analysis.

Healthcare professionals more often reported information concerning 'patient characteristics', but given the mean difference of 8.6%, we considered this finding negligible for daily pharmacovigilance practice. We saw the same pattern when analysing serious reports separately. However, for these cases, healthcare professionals scored the domain 'patient characteristic' significantly higher compared to patients, with a mean difference of 10.6%. Healthcare professionals might see more need to provide this type of information. Furthermore, in cases of hospitalization or death, healthcare professionals may include the hospital discharge letter with their report. This letter provides information about patient characteristics. For patients this hospital discharge letter is mostly not available.

Previous research about patient versus healthcare professional reporting demonstrated that overall, healthcare professionals reported more information related to the suspected drug, e.g. drug dosage and route of administration [21]. In the present study, information concerning the suspected drug was only relevant in a limited number of cases, such as a 'brand name in case of an ADR after drug substitution'. For these cases, mostly one subdomain was relevant for assessment of the report. Therefore, when this subdomain was present in the healthcare professional report

(score of 100%), but lacking in the patient report (score of 0%), this resulted in a difference of 100%. Consequently, the mean difference (30.8%) seems to be large but has no practical relevance.

As far as we are aware, this is the first study to use reports from the patient and the patient's healthcare professional on the same case. Due to this unique approach we were able to directly compare the differences in clinical information reported by both groups. There may have been some selection bias, as a report had to be 'interesting' enough for both patients and healthcare professionals to report it independently. The motivation or reason for reporting has to be considered when exploring to what extent our results are generalizable to reports of the Lareb database as well as to other pharmacovigilance centers. Healthcare professionals as well as patients report because of the severity of the reaction and wanting to contribute to medical knowledge [30]. Patients also report because they felt their complaints were not taken seriously elsewhere or because they already reported the ADR to a healthcare professional with no result [30]. Unfortunately we have no data on motives for reporting in the Lareb database. Regarding the generalizability, the overall characteristics male-female ratio and reported ADR (based on SOC classification) of the included reports are in line with previous studies [12,15,16,19,22,30-35]. Not surprisingly, our study set concerned 33.5% serious reports, which is a higher percentage than the average percentage of serious reports present in the Lareb database (average of 20% serious healthcare professional reports and 18% patients reports, from 2013-2015) [36]. Finally, we do not know to what extent the healthcare professional and patient discussed the case and whether this had an influence on the level of reporting information. Due to these bias, results should be generalized with caution.

Some methodological issues have to be addressed. In order to analyse the level of reporting clinical information, we used the clinical documentation (ClinDoc) tool [27]. This tool determined which information is relevant for a case and then assesses whether relevant information has been reported completely. Even though we used a standardized method of assessment, the level of clinical information remains a somewhat subjective measure, but using a structured approach was better than subjectively compare reports of patients and healthcare professionals. For the present study we tried to minimize variations between assessors by training assessors how to use the tool. Furthermore, each report was scored by two assessors individually and differences between domain scores were discussed until agreement was reached. In order to keep assessors 'blind' about the type of reporter (patient or healthcare professional) we had to remove some identifying information.

Reports by patients and healthcare professionals reflect their own experiences and perceptions of the ADR. The present study specifically compared the level of reporting clinical information. We did not capture all possible information that can

be reported in our study. Others for example, showed that patients report more about the impact of the ADR on their daily life compared to healthcare professionals [19,20,37,38]. This information is also valuable for pharmacovigilance practice. In our view, reports of both patient and healthcare professionals can contribute to an optimal pharmacovigilance.

CONCLUSION

In a unique study of cases of ADRs reported by patients and healthcare professionals we found that patients report clinical information at a similar level as their healthcare professional. For an optimal pharmacovigilance both healthcare professionals and patients should be encouraged to report.

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4

Contribution of patient reports to signal detection

4.1

Does patient reporting lead to earlier detection of drug safety signals?
A retrospective observational comparative study between adverse drug reaction reports by patients and healthcare professionals

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SUBMITTED

ABSTRACT

Objective: To explore if there is a difference between patients and healthcare professionals (HCPs) in time to reporting drug-adverse drug reaction (ADR) associations which led to drug safety signals.

Design: This was a retrospective observational comparative study about ADR reports by patients and HCPs on time to reporting of selected drug-ADR associations which led to drug safety signals.

Setting: ADR reports were selected from the World Health Organisation Global database of individual case safety reports, VigiBase.

Signals: Reports were selected by using 60 associations described in signals detected by the Netherlands Pharmacovigilance Centre Lareb between 2011 and 2015.

Main outcome measures: Primary outcome was the difference in time to reporting between patients and HCPs. The date of the first report for each individual signal was used as time zero. The difference in time between the date of the reports and time zero was calculated. Statistical differences in timing were analysed on the corresponding survival curves using a Mann-Whitney U test.

Results: In total 2822 reports were included, of which 52.7% were patient reports, with a median of 25% for all included signals. Overall, HCPs reported earlier than patients: median 7.0 vs 8.3 years ($p < 0.001$).

Conclusions: Patients contributed a large proportion of reports on drug-ADR pairs that eventually became signals. For all signals, median time to signal detection was 10.4 years. HCPs generally reported 1.3 year earlier than patients. These findings strengthen the evidence on the value of patient reporting in signal detection, and highlight an opportunity to encourage patients to report suspected ADRs even earlier in the future.

INTRODUCTION

Pharmacovigilance centres around the world have an important role to monitor the safety of drugs in the postmarketing phase. They collect information about adverse drug reactions (ADRs) spontaneously reported by healthcare professionals and patients, for example by the Yellow Card Scheme in the UK. Having patients directly reporting to the national pharmacovigilance centres is relatively new in most areas of the world. In 2012 in the European Union, it became mandatory by law for countries to give patients the opportunity to report possible ADRs directly to the competent authority, although a number of countries introduced reporting by patients earlier [1;2]. In some countries, like the USA, patients have already been able to report for decades. Reports from patients are a well-established source of information in drug safety [3]. Despite patient participation gaining more and more attention worldwide, this does not necessarily mean that countries have fully embraced patient reporting [4;5]. More experience and sharing of information between countries is needed to fully understand its value.

Studies already demonstrated that reports by patients positively contribute to pharmacovigilance. Patients generally give an adequate description of the course of clinical symptoms and they seem more likely to report on the impact of ADRs on their daily life compared to healthcare professionals [6;7]. Some studies found that patients are likely to report more serious ADRs compared to healthcare professionals, while others demonstrate the opposite [8-12]. There are also studies that demonstrated no difference between both groups [6;7;13;14]. Although there have been concerns about the quality of patient reports in the past, it has recently been shown that the clinical quality of information reported by patients is comparable to that of healthcare professionals [15]. Concerning the detection of new drug safety signals, it was demonstrated that reports by patient are taken into account [16-19]. These signals include ADRs not listed in the Summary of Product Characteristics (SPC) and new aspects of known ADRs. A recent study in the Netherlands exploring signals detected from 2010 to 2015 showed that the number of reports directly from patients in the signals rose from 16 (10% of total) in 2010 to 161 (28.3% of total) in 2015 [16]. There were 137 serious reports in all examined signals (30.8% of all patient reports) compared to 224 healthcare professional reports (19.2% of total reports).

Less is known about the difference in timing of reporting by patients and healthcare professionals. It has been suggested that reporting by patients contributes to an earlier detection of drug safety signals [20;21]. Indeed, a certain number of reports is necessary to generate new drug safety signals and reports by patients provide an additional source of information. In addition, patients may report earlier on certain ADRs compared to healthcare professionals; for the latter group one of the reasons for

not reporting a possible ADR to a pharmacovigilance centre may be the uncertainty that it actually concerns an ADR.

Little is known about the extent to which patient reports might impact on timely signal detection and whether this is different for ADRs classified as so called 'important medical events' (IMEs), defined as those events that result in death or require (prolonged) hospitalization, and those not classified as IMEs [22;23]. Furthermore, comparing the USA and Europe may provide additional insights given the extensive experience with patient reporting in the USA, versus Europe where patient reporting is relatively new. In the USA there has been a relatively constant flow of patient reports over time, while in most European countries the number of patient reports continues to rise [3;24;25]. Also, in the USA patient reports are mostly received through pharmaceutical companies, while in Europe patients mostly report directly to the national pharmacovigilance centre [2].

This study aims to explore if there is a difference between patients and healthcare professionals in time to reporting drug-ADR associations which led to drug safety signals. The secondary aims are to explore if there is a difference in time to reporting between patients and healthcare professionals for drug safety signals characterized as IMEs, and if there is a difference for reports from those regions with a long history of patient reporting (USA) versus a region with a short history of patient reporting (Europe).

METHOD

Study design and data source

This was a retrospective observational comparative study about ADR reports by patients and healthcare professionals on time to reporting of selected drug-ADR associations that were subsequently classified as drug safety signals. ADR reports were selected from the WHO global database of individual case safety reports, VigiBase. As of June 2017, this database contained over 15 million ADR reports received from over 120 member countries of the WHO programme for international drug monitoring [26].

We selected all reports of drug-ADR associations present in all drug safety signals detected by the Netherlands Pharmacovigilance Centre Lareb between 2011 and 2015. At Lareb, reports by patients were handled in the same way as those from healthcare professionals and they were fully integrated into the process of signal detection. During signal detection, qualitative aspects as well as quantitative aspects (disproportionality analysis) are taken into account [27;28]. Signals covered a wide

range of different ADRs. We excluded signals on drug interactions, multiple suspected drugs, and dosing or administration errors. All signals are publicly accessible on the Lareb website [29;30]. In total, 60 signals were included in this study.

Based on the drug-ADR associations present in the selected signals, ADR reports were selected from a frozen VigiBase version as of October 2015. Selection of reports in VigiBase was based on the WHO drug classification system, the ATC-5 code or the drug's brand name [31] and the Medical Dictionary for Regulatory Activities *MedDRA* Preferred Term coding [32], depending on the drug-ADR association described in the signal. The drug needed to be classified as 'suspected' or 'interacting' on the reports. Reports had to be filed in the database before dissemination of the drug safety signals.

Only reports that had the E2B structure, an international standard for transmitting ADR reports, were included. Only reports that were either pure patient reports (E2B reports with a single reporter whose qualification was 'Consumer or other non-health professional') or pure healthcare professional reports (E2B reports with a single reporter whose qualification was 'Physician', 'Pharmacist', or 'Other health professional') were included. There was no exclusion of duplicate reports; in case the event had been reported by different sources, these were all taken into account.

We only included data from countries if they accepted reports from patients at the time of the first report for the specific drug-ADR association in VigiBase. Start date of patient reporting in the specific countries was obtained from literature [2] or through personal contacts with the national pharmacovigilance centres. This was to ensure that countries not only formally accepted patient reports but actually did so in practice. We excluded data from countries with no patient reports in VigiBase. See Figure 1 for a flowchart of the Methods of data collection.

Outcomes

The primary outcome was the difference in time to reporting between patients and healthcare professionals. The secondary outcomes were the differences in time to reporting between patients or healthcare professionals for (i) IMEs versus non-IMEs, according to the European Medicines Agency (EMA)-list of Important Medical Events, according to MedDRA terminology [18], and (ii) for the USA versus Europe. For Europe, we included countries within the European Union, as well as Iceland and Norway because they participate in EMA regulatory decision making. Although Switzerland, does not participate in EMA regulatory decision making, this country accepts reports directly from patients since 2002 and shares a similar culture with the rest of Europe. For this reason, we decided to take Switzerland into account as well.

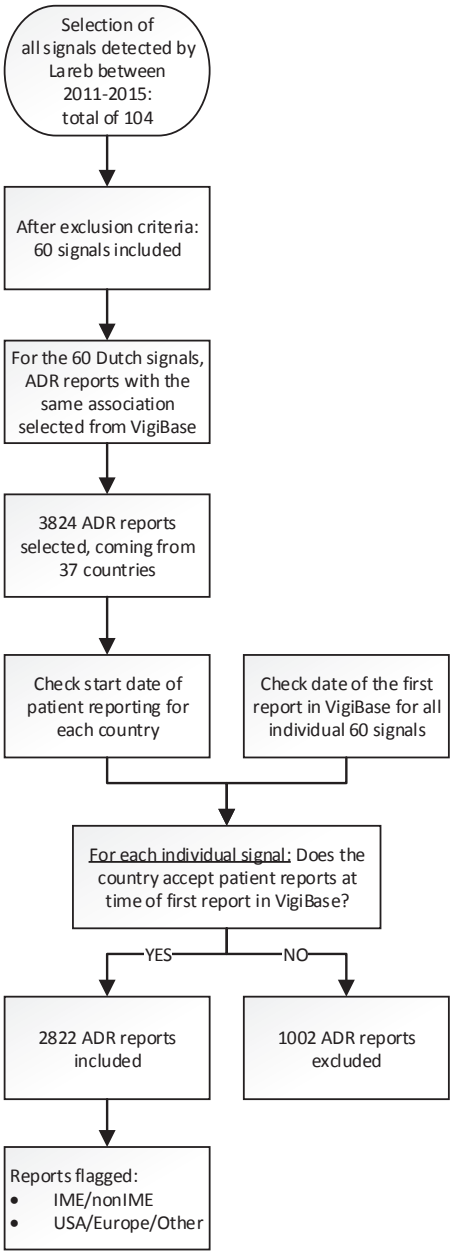

Figure 1. *Flowchart of the Methods of data collection*

Analysis

The date of the first report for each individual signal was used as time zero. All reports on the same drug-ADR association from time zero until signal detection were

included. We calculated the difference in time between time zero and the following reports from patients and healthcare professionals for each signal individually. Subsequently, data for all signals were pooled. The percentage of reports originating from patients was calculated and it was determined whether a healthcare professional or a patient made the first report for each signal.

Kaplan Meier plots were used to visualize the reporting over time by patients and healthcare professionals, respectively. Statistical differences in time to reporting between patients and healthcare professionals were explored on the corresponding survival curves using Mann-Whitney U tests. To investigate the secondary outcomes, sub-analyses were made for signals classified as (non)IMEs and reports from the USA and Europe. In addition, time to reporting was analysed for healthcare professionals in the USA versus Europe, and patients in the USA versus Europe. Statistical significance was based on a p-value less than 0.05. Data were analysed using the statistical software program SPSS Statistics, version 22.0 (SPSS, Chicago, IL).

There may be a large difference between reporting of the first report and the time to signal detection for the individual signals. To explore the meaning of the obtained difference in time to reporting between patients and healthcare professionals, relative differences defined as the difference in median time to reporting by patients and healthcare professionals divided by the total time until signal detection, were analysed. The difference in median between both groups was plotted against the total number of days until signal detection. For calculating the median, all signals with at least three patients and three healthcare professional reports were included.

RESULTS

Characteristics of included signals

In total 60 signals were included (Table 1). The median time to signal detection, calculated from the date of the first report for each individual signal, was 10.4 years, with an inter quartile range of 7.6 – 13.6 years. The signals included a total number of 2822 reports, of which 1488 (52.7%) were reported by patients and 1334 (47.3%) by healthcare professionals. The proportion of patient reports in the individual signals ranged from 0% to 84.4%, with a median of 25.0%. A total of 13 signals (21.7%) did not contain any reports from patients. For 12 signals (20.0%) the first report was made by a patient, for 48 (80.0%) by a healthcare professional.

A total of 18 (30.0%) signals were classified as IME (Table 1, signals in *italic*) [18]. Overall, IMEs included fewer reports from patients compared to healthcare professionals, range 0% – 55.1% (median of 7.2%) versus non-IMEs 0% – 84.4% (median

Table 1. *Description of the 60 drug safety signals*

Drug	ADR	Total number of reports	Number of healthcare professional reports	Number of patient reports	Mann-Whitney U test, p-value	Ratio†
Olanzapine	*Cerebrovascular accident*	185	83	102	0.058	0.06
Ciclosporin	*Posterior reversible encephalopathy syndrome*	127	98	29	0.126	-0.08
Gabapentin	***Blood glucose decreased and hypoglycaemia***	76	**58**	18	0.026	0.39
Aripiprazole	*Hypothyroidism*	28	**14**	14	0.016	0.68
Natalizumab	*Cervical dysplasia*	17	14	3	0.591	n.a.
Medroxyproges-terone	*Injection site necrosis and injection site atrophy*	30	28	2	1.00	n.a.
Proguanil hydrochloride/ Atovaquone	***Psychotic disorder***	11	9	**2**	0.036	n.a.
Aripiprazole	*Psychosis aggravated*	13	12	1	0.667	n.a.
Clindamycin	***Acute generalised exanthematous pustulosis***	8	7	1	0.250	n.a.
Ceftriaxone	*Hepatitis*	15	14	1	0.400	n.a.
Clarithromycin	*Angioedema*	26	25	1	0.077	n.a.
Hydroquinine	*Hypoglycaemia*	2	1	1	1.00	n.a.
Iobitridol	*Ventricular fibrillation*	1	1	0	n.a.	n.a.
Adalimumab	*Neuroendocrine carcinoma of the skin*	5	5	0	n.a.	n.a.
Nitrofurantoin	*Cutaneous vasculitis*	1	1	0	n.a.	n.a.
Tocilizumab	*Necrotising fasciitis*	6	6	0	n.a.	n.a.
Omeprazole	*Subacute cutaneous lupus erythematosus*	4	4	0	n.a.	n.a.
Fumaric acid	***Progressive multifocal leukoencephalopathy***	2	2	0	n.a.	n.a.
Lamotrigine	Alopecia	453	88	365	0.912	n.a.
Paroxetine	**Migraine**	176	35	**141**	0.002	-0.10
Tamsulosin	Vision blurred, visual acuity reduced and visual impairment	151	39	112	0.250	0.05
Escitalopram	**Headache**	235	128	107	0.140	0.06
Fluticasone	**Palpitations**	118	19	99	0.568	-0.01
Quetiapine	Paraesthesia	165	**84**	81	<0.001	0.20
Lamotrigine	**Nightmare**	77	12	65	0.099	-0.16
Levonorgestrel	Galactorrhoea	75	23	52	0.228	0.07
Quetiapine	Sleep apnoea syndrome	69	31	38	0.062	0.10
Omeprazole	Faeces discoloured	54	**17**	37	<0.001	0.35
Isotretinoin	**Erectile dysfunction**	59	28	31	0.331	0.12
Tamsulosin	**Dry mouth**	49	21	28	0.437	-0.05

Table 1. *(continued)*

Drug	ADR	Total number of reports	Number of healthcare professional reports	Number of patient reports	Mann-Whitney U test, p-value	Ratio†
Rivastigmine	**Nightmare and abnormal dreams**	33	13	20	0.137	0.20
Tamsulosin	Depression and depressed mood	30	12	18	0.368	0.08
Doxycycline	Paraesthesia	49	32	17	0.179	-0,15
Sitagliptin	Dyspnoea	135	**121**	14	<0.001	0,25
Dutasteride	**Testicular pain**	20	6	14	0.659	-0,11
Metronidazole	Oedema peripheral	35	24	11	0.958	0,00
Doxycycline	Skin discolouration, skin hyperpigmentation and pigmentation disorder	18	8	10	0.122	0,09
Terbinafine	Anosmia. parosmia. hyposmia	43	36	7	0.392	-0,14
Trazodone	Urinary incontinence	24	18	6	1.00	-0,56
Isotretinoin	Anal fissure	15	9	6	0.864	-0,12
Omeprazole	Erectile dysfunction	14	9	5	0.518	0,01
Azathioprine	Chromaturia	12	8	4	0.683	0,16
Metronidazole	Tongue discolouration	8	4	4	1.00	0.06
Azathioprine	Photosensitivity reaction	13	9	4	0.825	0,04
Tramadol	Anorgasmia	6	2	4	0.267	n.a.
Fluconazole	Drug eruption	31	28	3	0.875	0.04
Tramadol	Hiccups	12	9	3	0.282	0.04
Methylphenidate	Epistaxis	19	17	2	0.140	n.a.
Pandemrix	Injection site discolouration	4	3	1	1.00	n.a.
Duloxetine	Electric shock sensation	6	5	1	0.667	n.a.
Lenalidomide	Psoriasis	4	3	1	1.00	n.a.
Mirtazapine	Urinary retention	27	26	1	0.296	n.a.
Nadroparin	Headache	10	9	1	0.200	n.a.
Terbinafine	Hypoacusis	1	1	0	n.a.	n.a.
Desloratadine	Increased appetite	3	3	0	n.a.	n.a.
Mercaptopurine	Photosensitivity reaction	2	2	0	n.a.	n.a.
Buprenorphine	Skin depigmentation	2	2	0	n.a.	n.a.
Prednisolone	Hiccups	4	4	0	n.a.	n.a.
Betahistine	Hallucination	2	2	0	n.a.	n.a.
Terbinafine	Erectile dysfunction	3	3	0	n.a.	n.a.

Signals are sorted from IME signals to non-IME signals. And within the IME and non-IME signals they are sorted from highest number of patient reports to lowest

† Ratio calculated by: the difference in median days between reports by patients and healthcare professionals divided by the number of days until signal detection

Signals in *italic*: classified as Important Medical Events (IMEs)

Signals in **bold**: first ADR report was made by a patient

In case of $p<0.05$ the group of reporters that reported earlier is made **bold**

n.a.is not applicable

of 34.0%). The first report was made by a patient for 4 IMEs (22.2%) and 8 non-IMEs (19.0%).

Patient reports were from 24 different countries: Belgium, Bulgaria, Canada, the Democratic Republic of the Congo, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Iceland, Morocco, the Netherlands, Norway, Peru, Portugal, Slovakia, Sweden, Switzerland, Turkey, United Kingdom, and the USA. A total of 2124 reports came from the USA (61.9% patient reports) and 430 from Europe (21.9% patient reports) and 268 from non-European countries. For reports from the USA, 26.8% of the healthcare professional reports were classified as IMEs and 7.2% of the patient reports. For reports from Europe, 25.4% of the healthcare professional reports were classified as IMEs, and 37.2% of the patient reports.

Comparison in time to reporting

The overall cumulative distribution of time to reporting of patients and healthcare professionals is shown in Figure 2. The corresponding Mann-Whitney U test suggested that there was a statistically significant difference between these distributions ($p<0.001$). Healthcare professionals generally reported earlier than patients with a median time to reporting of 7.0 vs 8.3 years, and corresponding interquartile ranges of respectively 3.9 – 9.5 and 6.2 – 10.4 years. For IMEs, healthcare professionals and patients took a median time to reporting of 6.9 vs 8.1 years and for non-IMEs 7.0 vs 8.2 years (Figure 3a-b). In both cases, there was an overall statistically significant difference in the time distribution ($p < 0.001$). The cumulative distributions of reports from the USA and Europe are shown in Figure 4a-b. For the USA, median time to reporting for healthcare professionals and patients was 6.0 vs 8.1 years and for Europe 7.8 vs 7.9 years. The corresponding tests for distribution differences were both significant, $p<0.001$ and $p=0.03$, respectively. In addition, healthcare professionals

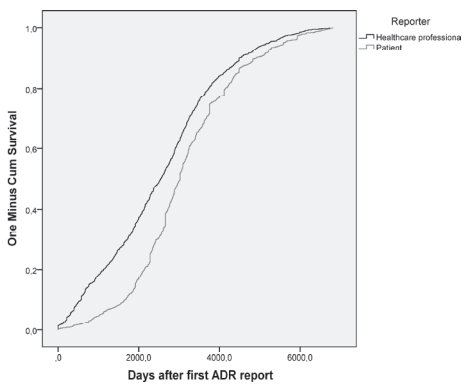

Figure 2. *The cumulative distribution of time of ADR reports, after the first ADR report, coming from patients and healthcare professionals, Mann-Whitney U p-value <0.001*

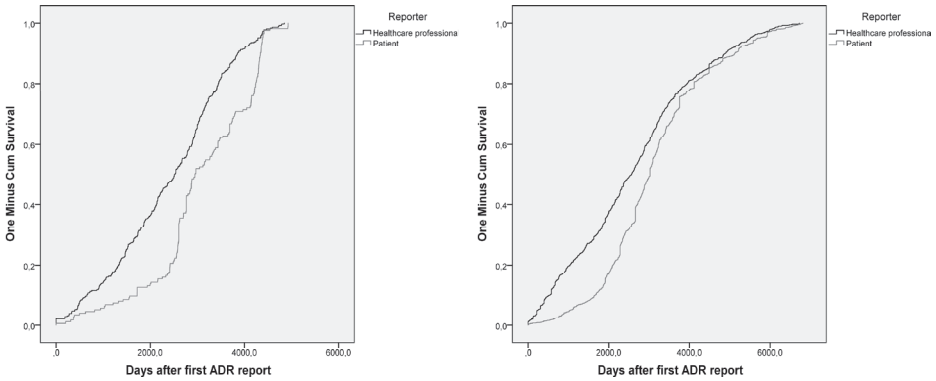

Figure 3a-b. *The cumulative distribution of time of ADR reports, after the first ADR report, coming from patients and healthcare for:*
a) IMEs, Mann-Whitney U p-value <0.001
b) non-IMEs, Mann-Whitney U p-value of <0.001

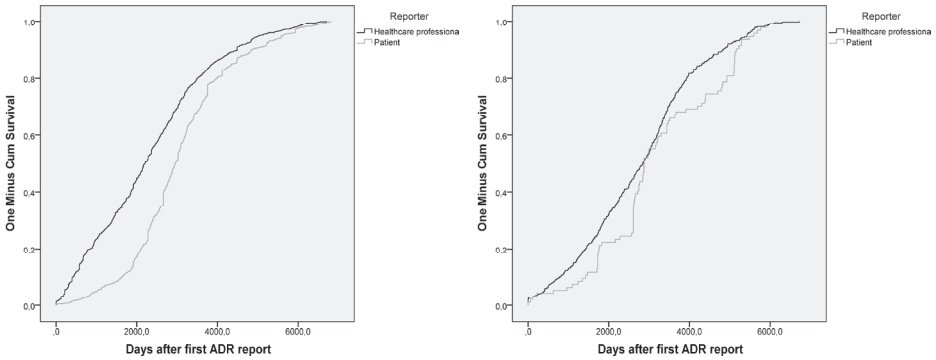

Figure 4a-b. *The cumulative distribution of time of ADR reports, after the first ADR reports, coming from patients and healthcare for:*
a) study cases coming from the USA, Mann-Whitney U p-value <0.001
b) study cases coming from Europe, Mann-Whitney U p-value of 0.03

in the USA reported earlier compared to those in Europe (p<0.001). For patients, no statistically significant difference was shown (p=0.531).

Individual signals

The analysis of the individual signals showed that for seven signals a statistically significant difference in time to reporting between the two groups was present (Table 1). For two of these signals, patients reported significantly earlier than healthcare professionals: 'paroxetine associated with migraine' (p=0.002) and 'proguanil hydrochloride/atovaquone associated with psychotic disorder' (p=0.036).

To explore the meaning of the differences in time to reporting between patients and healthcare professionals, the difference in median days between reports by patients

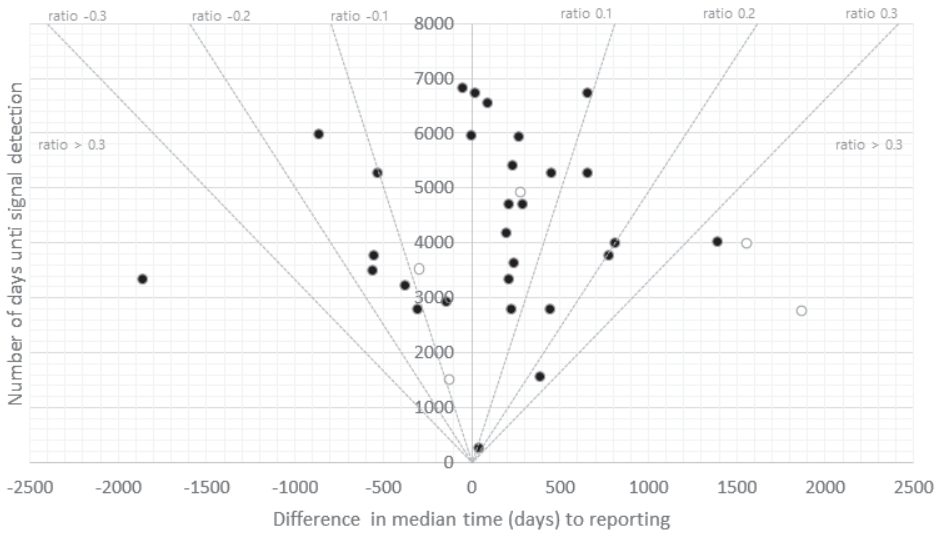

Figure 5. *Scatterplot of the difference in median days between reports by patients and healthcare professionals divided by the number of days until signal detection, plotted against the number of days until signal detection*

closed bullet = signal classified as non-IME; open bullet = signal classified as IME

The ratio was calculated by the difference in median divided to the number of days until signal detection. A positive ratio means earlier reporting by healthcare professionals and a negative ratio earlier reporting by patients.

and healthcare professionals divided by the number of days until signal detection, was plotted against the number of days until signal detection (see Figure 5). A positive ratio means earlier reporting by healthcare professionals and a negative ratio earlier reporting by patients. The ratio-lines in the figure give an indication of the meaning of the difference in median between both groups. A small ratio in combination with a high number of days until signal detection indicated little clinical relevance, while a high ratio in combination with a small number of days until signal detection indicated a higher level of clinical relevance. In total, 34 signals were included in the scatter plot, of those 5 were classified as IMEs and 29 as non-IMEs. 19 out of 34 signals had a ratio between -0.1 and 0.1; 3 of those signals were classified as IMEs and 16 as non-IMEs. For 1 signal there was no difference between patients and healthcare professionals, for 11 signals, patients reported earlier and for 22 healthcare professionals reported earlier. For patients, there was 1 signal with a ratio of less than -0.3. For healthcare professionals, there were 3 signals with a ratio over 0.3, including 2 classified as IMEs.

DISCUSSION

With the upcoming interest in patients as stakeholders in pharmacovigilance, it is important to explore the impact of patient reporting on early detection of new drug safety signals in pharmacovigilance. We demonstrated that ADRs which led to drug safety signals were generally reported earlier by healthcare professionals than patients, with an overall median difference of 1.3 years. This difference was present for ADRs classified as IMEs as well as non-IMEs. Although for the USA a difference in timing between both groups was present, for Europe the difference was negligible. The ratios in time to reporting were small, indicating that the difference in time to reporting ADRs between patients and healthcare professionals had limited impact on the overall time to signal detection for most signals.

It has been suggested that patient reports might enable earlier signal detection [20;21]. In 1996, *Egberts et al.* compared information obtained from patients and healthcare professionals on the, at the time, new antidepressant paroxetine [21]. At that time in the Netherlands, patients were not yet able to report directly to the pharmacovigilance centre, but could consult a telephone medicines information service maintained by pharmacists. Comparing the timing of reports by healthcare professionals to the national pharmacovigilance centre with questions by patients to the telephone service, showed that patients posted questions to this telephone service earlier as compared to healthcare professionals, with a mean time lag for all suspected reactions of 229 days. *Hammond et al.* explored time to signal detection for four randomly selected GlaxoSmithKline (GSK) marketed drugs, for reports of patients and healthcare professionals combined and as separate groups [33]. Using disproportionality analysis, 23 signals of disproportionate reporting were identified, of which 52.2% (12 of 23) at an earlier stage when the patient reports were included, 34.8% (8 of 23) in the same year and 13% (3 of 23) later when patient reports where included. The aforementioned studies focussed on time-aspects of statistical drug-ADR reporting associations not necessarily representing safety signals. To our knowledge, including actual drug safety signals to compare time to reporting between patients and healthcare professionals has not been explored before.

In order to find a new drug safety signal, a certain amount of reports is necessary. The introduction of direct patient reporting introduced a growth in the number of reports by patients. This growth also reflects in the number of patient reports that contributed to new drug safety signals [16]. In the current study, we found a relatively high proportion of patient reports in the included signals; 52.7% of all reports and a range of 0% to 84.4% for the individual signals. Reports by patients are more represented in ADRs classified as non-IMEs than IMEs; range of 0% – 84.4% versus

0% – 55.1% respectively. Analysing signals individually, we demonstrated that for some, patients were earlier in reporting, and for others healthcare professionals. It is for this reason plausible that reports by patients can contribute to earlier signal detection. There are some points to consider concerning the data used for this study. In our study, over 60% of the reports from the USA originated from patients. This was higher than in another analysis from the USA, which showed that from 2006 to 2014 an average of 47% of all reports were from patients [3]. This may be explained by the nature of the selected signals. It was furthermore striking that the percentage reports classified as IME was higher for patient reports from Europe compared to those coming from the USA. The percentage IMEs included in all patient reports was in line with previous results of a study on Dutch drug safety signals by *van Hunsel et al*. They showed that of all reports by patients that contributed to a signal in the Netherlands from 2010 to 2015, 30.5% included an ADR classified as IME. This was a higher percentage than reports by healthcare professionals (22.5%) [16].

By selecting reports from the international database VigiBase, we could include a high number of reports which allowed us analysing signals by importance of the event and by region of origin. It must be kept in mind that data pooling can influence the outcome. On average, the median time to signal detection, calculated from time zero, was 10.4 years. Given the large variation in number of reports per signal, signals with a lot of reports contributed to a larger extent to the overall outcome. To place our results in perspective, we therefore also explored all signals individually.

The reporting rate may vary over time and may differ between patients and healthcare professionals. It can be influenced by factors, such as media attention or discussions on the internet [34;35]. As far as we know, there was no specific media attention for the drug-ADR associations included in our study, but differences in timing due to external factors cannot be ruled out. In addition, for Europe due to changes in the pharmacovigilance legislation in 2012, it is possible that this legal change caused a steeper growth in patient reporting compared to healthcare professional reporting. This may have contributed to the difference in time to reporting we found between healthcare professional reports from the USA versus Europe.

CONCLUSION

Patients contributed a large proportion of reports on drug-ADR pairs that eventually became drug safety signals; 53% overall, with a median of 25%. This corroborates earlier findings on the contribution of patient reports to signal detection in pharmacovigilance. For all signals, median time to signal detection was 10.4 years. Healthcare

professionals generally reported 1.3 year earlier than patients. This was the case for ADRs classified as IMEs as well as non-IMEs. This highlights an opportunity to further increase the value of patient reporting in the future, by encouraging patients to report suspected ADRs earlier.

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5

Practice of pharmacovigilance

5.1

Feedback for patients reporting adverse drug reactions; satisfaction and expectations

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ABSTRACT

Background: Due to the rising number of patient reports in pharmacovigilance, the manner in which feedback is provided to patients is an element to be considered.
Objective: To explore the satisfaction of patients towards personalized and general feedback in response to their reported adverse drug reactions (ADRs).
Methods: Patients who reported an ADR to the Netherlands Pharmacovigilance Centre Lareb for the first time in the period between October 2012 and April 2013 were included. Reporters received personalized feedback or a general acknowledgement letter. Satisfaction towards the received feedback, expressed on a 5-point Likert scale (1 very good to 5 very poor), was studied using a web-based questionnaire. Data were analysed using Pearson Chi-square test and linear regression analysis. Statistical significance was based on $p<0.05$.
Results: A total of 471 patient-reporters were contacted with a total response of 52.5%. Respondents of both groups were satisfied with the received feedback, average score 2 (good). Respondents of the personalized feedback-group were however more satisfied score 2.0 versus 2.5 (p-value <0.001) and considered the feedback more clear and useful compared to respondents of the acknowledgement letter-group, respectively score 1.6 versus 1.7 (p-value 0.01) and score 2.1 versus 2.5 (p-value <0.001).
Conclusion: Patients reporting ADRs are satisfied with feedback received from the pharmacovigilance centre, whether this is a personalized feedback or a general acknowledgment letter. They find it clear, useful and it meets their expectation. Although differences were found between the two types of feedback, these differences did not indicate dissatisfaction towards the received feedback.

INTRODUCTION

A pharmacovigilance centre aims at the timely detection of possible new drug safety signals. The dissemination of knowledge they generated from incoming spontaneous reports is an important aspect of their work. This can be achieved for example by (inter)national publications about adverse drug reactions (ADRs), maintaining a website with information and providing training. Another way of providing feedback, but also to increase the involvement of reporting healthcare professionals and patients, is to send dedicated personalized feedback in response to their reported ADR. In the Netherlands, reporters are able to choose on the reporting form if they wish to receive a personalized feedback or not. For healthcare professionals this feedback on the reported association contains information based on the Summary of Product Characteristics (SPC) of the drug, information found in literature and information about previous reports in the Dutch pharmacovigilance database (time to onset, de- and rechallenge, causality) [1]. For patients, having been able to report in the Netherlands since 2003, the feedback is less elaborate compared to the feedback sent to healthcare professionals but basically contains the same elements. Furthermore, the feedback is written in lay-man's language.

In addition to providing information, a personalized feedback may aim to create a relationship between the pharmacovigilance centre and the reporter. This relationship can contribute positively to obtain follow-up information [1]. This applies to both, healthcare professionals and patients.

A personalized feedback may also influence the reporting rate positively [1-3]. This mainly applies for healthcare professionals. They can apply this newly obtained information about the risk of a drug for the future treatment of their patients [4]. *Wallerstedt et al.* explored if the content of the feedback sent to doctors would influence the reporting rates [3]. They used two different feedback alternatives, one standard feedback and one feedback supplemented with information on the reported drug-ADR association. Many doctors (70%) stated that the content of the feedback would affect their willingness to report ADRs. The importance of a personalized feedback for healthcare professionals was also explored in the Netherlands [1]. A questionnaire survey among 1200 pharmacists, general practitioners and medical specialists revealed that most of the responders would be (very) unsatisfied if they would only receive an acknowledgement letter instead of a personalized feedback. A personalized feedback was considered to be (very) important for motivating them to report an ADR in the future. A large proportion of the responders (80%) stated that the personalized feedback increased their knowledge.

There has been a growing interest in the role of patient reporting of pharmacovigilance [5]. Feedback provided to patients mostly consists of an (automatically

generated) acknowledge letter after they have reported an ADR. Sending a personalized feedback with information about the reported ADR to patients is not common practice for many pharmacovigilance centres. An 11-country survey focused on the experience with patient reporting showed that only a few countries (New Zealand, Malaysia, Australia and the Netherlands) send personalized feedback to patients [6]. By sending a personalized feedback to patients they will not only be informed about the drug-ADR association, but also offers the opportunity to refer a patient when the reported symptoms might indicate a more serious problem where a consultation with a healthcare professional may be warranted.

From literature it is known that patients would like to receive information in response to their reported ADR [7,8]. A previous study from the Netherlands showed that 44.8% of patients reported an ADR because they wanted additional information from the pharmacovigilance centre [8]. Information desired by patients is an acknowledgement on their report and information about the reaction or the drug they reported about. Further they would like to receive information about the frequencies in which other similar reports had been received, how common the ADR is, advice on what to do and if any action would take place as a result of their report [7].

The introduction of the new European pharmacovigilance legislation in 2012 allows patients of all European Union member states to report their ADRs directly to the competent authorities [9]. Pharmacovigilance centres who were previously unfamiliar with patient reporting, may now be confronted with (a high number of) patient reports. In the Netherlands, the number of patient reports continuous to rise with 173 reports in 2003 (4.0% of total), 1545 in 2010 (15.6% of total), 2602 reports in 2012 (18.3% of total) and 3960 (23.3% of total) in 2013 [10-12]. Experiences of the Netherlands Pharmacovigilance Centre Lareb show that writing a personalized feedback to patients can be time consuming. The level of education of the patients is mostly unknown so that all information must be written in layman's terms. Given the nature of the reports, the wording also requires more empathy compared to healthcare professional reports.

Feedback to patients, whether personalized or not, should be clear and considered useful by a patient. Clarity of the received information, combined with usefulness and expectations, may determine how satisfied a patient is with the provided feedback. Literature lacks information about patients' satisfaction towards feedback they received in response to their reported ADR. It may be that not the content of the given information, but rather the fact that a feedback is send, makes patients feel satisfied. The aim of this study is to explore the satisfaction of patients towards feedback they received by the Netherlands Pharmacovigilance Centre Lareb in response to their reported ADRs. In addition, information desired by patients in general is explored.

METHOD

Study design

An electronic questionnaire among patients who reported non-serious ADRs.

Study population

The study population consisted of all patients who for the first time reported a possible ADR to the Netherlands Pharmacovigilance Centre Lareb in the period between 1 October 2012 and 1 April 2013 by means of the electronic reporting form. In the Netherlands, the spontaneous reporting system is maintained by the Netherlands Pharmacovigilance Centre Lareb. Patients and healthcare professionals are able to report by means of a paper and electronic reporting form. The pharmacovigilance centre is an independent foundation, which works in close collaboration with the Medicines Evaluation Board (MEB) and informs the MEB of drug safety signals. In the past the Netherlands Pharmacovigilance Centre worked with several regional centres, however since 2010 there is only one national centre. The use of the electronic form is encouraged and used by 98% of all reporters [12]. In order to prevent that patients were previously informed about the possibility to receive feedback, the option to request personalized feedback was removed from the patient reporting form prior to the study.

The study population was divided into two groups. One group received a personalized feedback (personalized feedback-group), the other group received an acknowledgement letter (letter-group). An example of the personalized feedback and the general acknowledgement letter is shown in Table 1. Lareb carries out a 'triage' with incoming reports in order to distribute the ADR reports over several specialized assessors [6]. Division of the reports into the two study groups was done alternately during the triage-process.

Lareb has an electronic system for sending feedback to reporters. The acknowledgement letter is automatically sent to the reporter once the assessor finished the report. If the reporter is in the letter-group, the assessor formulated a personalized feedback. This feedback is automatically inserted into the standard acknowledgment letter.

Reported ADRs can be serious or non-serious, according to international CIOMS criteria [13]. ADRs considered serious include reactions leading to (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events, congenital abnormalities. Prior to the study it was decided that reporters of serious ADRs should always receive a personalized feedback in order to give additional information. The same applies for reporters who specifically asked a question in the

Table 1. *Example of a feedback for patients*

Example of personalized feedback	Example of general acknowledgement letter
Dear (name reporter), *Thank you for reporting to the Netherlands Pharmacovigilance Centre Lareb. Your report has been registered under the number 12345.* *Lareb recently published about aggressive behaviour during the use of antidepressant medication (SSRIs). Aggressive behaviour is described in the official information leaflet of fluoxetine. This reaction is mainly seen in users under 18 years. The type of adverse drug reactions and the extent to which they occur varies per person. Unfortunately this cannot be predicted. Recovery of the aggressive behaviour after withdrawal of fluoxetine may be indicative of a causal relation between the drug and the drug and the aggressive behaviour.* *Your report will be included in the Lareb database. This is a database in which all adverse drug reactions of all drugs in the Netherlands are collected. This enables Lareb to gets a good impression of the safety of medicines and will take action if necessary.* *Thank you again for reporting.* *Best regards,*	*Dear (name reporter),* *Thank you for reporting to the Netherlands Pharmacovigilance Centre Lareb. Your report has been registered under the number 12345.* *Your report will be included in the Lareb database. This is a database in which all adverse drug reactions of all drugs in the Netherlands are collected. This enables Lareb to gets a good impression of the safety of medicines and will take action if necessary.* *Thank you again for reporting.* *Best regards,*

narrative on the reporting form, ADRs for which referral to a healthcare professional was deemed necessary in the view of the ADR assessor and ADR reports with possible legal consequences, e.g. reports that indicate the patient wants to make a legal complaint against the doctor. For that reason, these reports were excluded from this study.

Questionnaire development

A web-based questionnaire was designed and sent using the Survey Monkey package [14]. Questions were posed about:

- socio-demographic characteristics;
- expectations about what the pharmacovigilance centre would do with their report (processing);
- usefulness, clarity, expectations and satisfaction of the feedback;
- previous experience with reporting.

A closed format with 5-point-Likert scale was used in which response could be rated from very good (1) to very poor (5). A Likert scale may be used to attribute responses in one of a number of ranked categories. An underlying, continuous variable denoting individuals' degrees of agreement is mapped into categories that are ordered but are separated by unknown distances [15]. For this study we made the assumption that the distance between the categories is approximately equal.

Questions about patient characteristics and the satisfaction about the feedback were mandatory. For the questionnaire, see Appendix 1. In a pilot, the questionnaire was first tested in a small group of consumers (n=8) who were not familiar with the personalized feedback and were not involved in the study. The questionnaire was revised on the basis of the feedback received.

Sending the questionnaire

An invitation e-mail to participate in the questionnaire-study was sent to all patients who received a personalized feedback or an acknowledgement letter in the previous week. A reminder was sent to all non-responders two weeks after the invitation. Collection of the responses was finished four weeks after the first invitation was sent.

The link in the invitation e-mail was uniquely tied to the survey and the respondent's e-mail address. Therefore, the message could not be forwarded by respondents and only response per e-mail address was allowed. For this study Ethics committee approval was not required, as Dutch legislation does not request this for studies which do not affect the patient's integrity [16]. Participant data were sampled and stored in accordance with privacy regulations.

Data analysis

A Pearson Chi-square (Chi^2) test was performed to explore differences between responders and non-responders on the basis of gender, age and education. Respondent views on usefulness, clarity, expectations and satisfaction of the received feedback as expressed on the 5-point Likert scale were tested using linear regression analysis.

The questionnaire included a question if the received feedback was read by the reporter. When the reporter did not read or does not remember reading the received feedback, their response was excluded from the part of the analysis about the satisfaction of the received feedback. Statistical significance was based on $p<0.05$. Data were analysed using the statistical software program SPSS Statistics, version 20.0 (SPSS, Chicago, IL).

Experiences with reporting and desirable information

In order to explore experiences with reporting and information that is desired by patients in general, these questions were added to the questionnaire. In addition,

these questions were also asked to reporters of serious ADRs in order to obtain an overall view of information desired by patients. No comparison was made between the groups. Questions about experiences with reporting were dichotomous. Easiness of reporting was scored on a 5-point Likert scale.

Responses to open question about information that is desired were analysed by two researchers (FH, LR) individually using content analysis. Content analysis requires the creation of a list of categories derived from the data collected, and then systematically coding into these categories [17]. Differences were discussed until overall agreement was achieved. Data were analysed using descriptive statistics.

RESULTS

Response

A total number of 471 patient-reporters were contacted by e-mail, see Figure 1. A personalized feedback was send to 217 patients, of which 123 (56.7%) responded. An acknowledgment letter was send to 245 patients, of which 122 (48.3%) responded. There was a total response of 52.5%.

There were 8 (6.5%) respondents of the personalized feedback-group and 18 (14.8%) of the letter-group who indicated that they did not read or do not remember reading the received feedback. In total 115 (93.5%) respondents of the personalized feedback-group and 105 (86.1%) of the letter-group were included in the linear regression analysis.

Respondent characteristics

The respondent characteristics are shown in Table 2. No statistically significant differences were found for gender, age and education between the personalized feedback-group and letter-group.

Analysis of satisfaction towards received feedback

Results of the analysis of differences in usefulness, clarity, expectations and satisfaction between the feedback and letter group are shown in Table 3. Overall score for satisfaction – including clarity, usefulness, expectations and satisfaction – is *good* (score 2.0) for both groups. However, linear regression analysis demonstrated that respondents of the feedback-group are more satisfied, score 2.0 versus 2.5 (p-value <0.001) and find the personalized feedback more clear and useful compared to respondents of the letter-group, respectively score 1.6 versus 1.7 (p-value 0.01) and score 2.1 versus 2.5 (p-value <0.001).

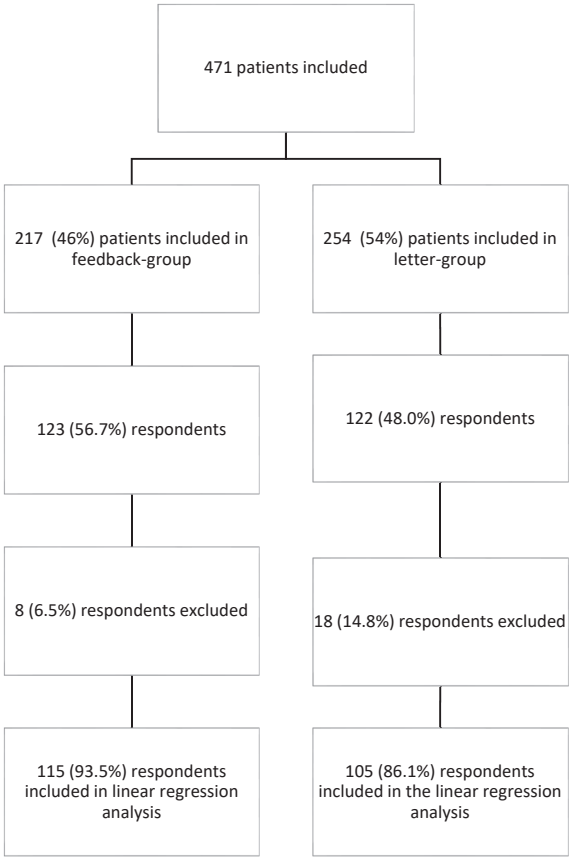

Figure 1. *Flowchart of number of respondents to the questionnaire*

Experience with reporting

In order to explore experiences with reporting and information that is desired by patients in general, this question was, in addition to the study population, also sent to 349 reporters of serious ADRs, of which 175 (50.1%) responded. Of all respondents 49.7% expected a reaction from the pharmacovigilance centre in response to their ADR report. Linear regression analysis showed no statistically differences in usefulness, clarity, expectations or satisfaction between respondents who did or did not expect feedback. Overall, 76.8% of the respondents found it (very) easy to complete the reporting form, 5.2% found it (very) hard and 3.3% indicated that they needed assistance in completing the reporting form. Of the respondents, 83.3% indicated that they experienced the ADR themselves while 12.3% reported for someone else. Of all respondents 87.4% would report again and 86.0% would encourage others to report ADRs.

Table 2. *Respondent characteristics*

Variables	Number in personalized feedback-group, (%)	Number in letter-group, (%)	Total	Chi² p-value
Gender				
Male	40 (32.5%)	38 (31.3%)	78 (31.8%)	0.82
Female	83 (67.5%)	84 (68.9%)	167 (68.2%)	
Age				
18-35	18 (14.6%)	14 (11.4%)	32 (13.1%)	0.32
36-65	66 (53.6%)	77 (63.1%)	143 (58.4%)	
> 65	39 (31.7%)	31 (25.4%)	70 (28.6%)	
Education				
Primary school	2 (1.6%)	1 (0.8%)	3 (1.2%)	0.20
Secondary school	17 (13.8%)	15 (12.3%)	32 (13.1%)	
Vocational school	35 (42.3%)	48 (39.3%)	83 (33.9%)	
Higher prof. education	52 (42.3%)	36 (29.5%)	88 (35.9%)	
Academic	17 (13.8%)	22 (18.0%)	39 (15.9%)	

Table 3. *Usefulness, clearness, expectations and satisfaction of the received feedback*

Group	Average score (1 very good to 5 very poor)	Linear regression analysis p-value	1. Very good number responders (%)	2. Good number responders (%)	3. Neutral number responders (%)	4. Poor number responders (%)	5. Very poor number responders (%)
Clarity of the feedback							
Personalized feedback	1.6		61 (53.0%)	47 (40.9%)	7 (6.1%)	0 (0.0%)	0 (0.0%)
Letter	1.7	0.01	34 (32.4%)	64 (61.0%)	7 (6.7%)	0 (0.0%)	0 (0.0%)
Usefulness of the feedback							
Personalized feedback	2.1		36 (31.3%)	46 (40.0%)	27 (23.5%)	3 (2.6%)	3 (2.6%)
Letter	2.5	<0.001	5 (4.8%)	49 (46.7%)	41 (39.0%)	10 (9.5%)	0 (0.0%)
Meets the feedback to expectations							
Personalized feedback	1.9		61 (53.0%)	20 (17.4%)	20 (17.4%)	12 (10.4%)	2 (1.7%)
Letter	2.0	0.56	49 (46.7%)	15 (14.3%)	35 (33.3%)	5 (4.8%)	1 (1.0%)
Satisfaction with the feedback							
Personalized feedback	2.0		45 (39.1%)	36 (31.3%)	27 (23.5%)	6 (5.2%)	1 (0.9%)
Letter	2.5	<0.001	5 (4.8%)	53 (50.5%)	41 (39.0%)	6 (5.7%)	0 (0.0%)

Desirable information

The open question about desirable information was answered by 48.1% of all respondents. Information that was mostly desired (20% of the respondents) was information about processing of the report and the causality of the drug-ADR association. Information about the frequency of the ADR was wished for by 14% of the respondents. Other desirable information that was mentioned (less than 10% for each item): information about recovery of the ADR, an acknowledgement of receipt, advice for further treatment and information about actions that took place in response to their report, for example further research.

DISCUSSION

This study showed that patients who reported non-serious ADRs are satisfied with a general acknowledgement letter as well as with a personalized feedback. This finding indicates that sending a general acknowledgement letter to patients who reported non-serious ADRs can be used by pharmacovigilance centres to provide feedback for patients in a way that ensures that they are informed about ADR reporting in general and satisfied with the service provided. We believe that feedback for patients may also be useful for positively reinforcing reporting of patient reported outcomes of ADRs in other setting, for pre- as well as post-approval studies, as described by *Banjerjee et al.* in the Patient-Reported Outcome Measures in Safety Event Reporting (PROSER) Consortium [18].

Sending a feedback to reporters is useful to increase knowledge about ADRs, to build a relationship with the reporter and it may also influence the reporting rate positively. Lack of time and the rising number of patient reports made us explore ways of providing feedback for patients in a more efficient way. This study indicates that a general acknowledgement letter may be used for such purpose. Analysis shows that respondents who received a personalized feedback assigned higher scores for *clarity*, *usefulness* and *satisfaction* compared to respondents who received an acknowledgment letter. This might be due to the fact that the personalized feedback contains more information desired by patient, e.g. information about the drug-ADR association and the frequency of the ADR. It is however questionable to what extent these differences are also relevant in practice.

The currently used acknowledgement letter is rather basic and doesn't contain much additional information desired by patients, as found in this study and described in literature [7]. Although an acknowledgment letter cannot contain information about the specific drug-ADR association about which was reported, it can be expanded with information desired by patient, for example: information about handling of their

report and action of the pharmacovigilance centre, whether or not the patient will be contacted, advice against self-management of drug use and general information to consult their healthcare professional if they have further questions or complaints.

Strengths and weakness

The study population comprised of 'new' patient-reporters, which ensured that patients were not biased by a previous experience with reporting and receiving feedback. Misclassification by previous knowledge of the patient about the personalized feedback was therefore not to be expected. A web-based questionnaire was used which is a simple and inexpensive way to explore patient views and satisfaction. In the Netherlands most people have access to the internet. Statistics Netherlands reports that 94% of the Dutch households (at least one person between age 16 – 74) had Internet access in 2011 [19]. As said, of all reports reported to Lareb in 2012, 98% were reported by the electronic reporting form [12]. The risk of selection bias is therefore considered to be low.

Comparison of the study population with an earlier study by Lareb, exploring patient's motivation for reporting ADRs, showed similarity for the ratio of gender, age and education [8]. Comparing the level of education with the Dutch population shows that respondents are higher educated; 33% higher prof. education/academic in Dutch population in 2011 versus 52.7% of the responders [20]. This should be taken into account when using the results of this study for other countries.

For the Netherlands Pharmacovigilance Centre Lareb this study helped to make decisions about a change in the manner of providing feedback to patients. Although there was a statistically significant difference in satisfaction between patients who received an acknowledgement letter versus a personalized feedback, the responses were still in the same range of satisfaction (score 2.0 versus 2.5). By also exploring information desired by patient in general, this study enabled us to draft a comprehensive acknowledgement letter for patients, see Appendix 2.

CONCLUSION

Patients reporting non-serious ADRs are satisfied with feedback received from the pharmacovigilance centre, whether this is a personalized feedback or a general acknowledgement letter. They find it clear, useful and it meets their expectation. Although differences were found, these differences did not indicate dissatisfaction towards the received feedback.

This study shows that for patients who reported a non-serious ADR, an acknowledgment letter can be used by pharmacovigilance centres to provide feedback in a

way that ensures that they are informed about ADR reporting in general and satisfied with the service provided.

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APPENDIX 1. QUESTIONNAIRE

General questions

1. Overall: age, gender and education of the participant.
2. Did you expect a reaction in response to your reported adverse drug reaction?*

Personalized feedback or acknowledgement letter

As a response to your reported adverse drug reaction the Netherlands Pharmacovigilance Centre Lareb sent you a personalized feedback/acknowledgement letter. The following questions will be about this personalized feedback/acknowledgement letter.

3. Did you read the personalized feedback/acknowledgement letter?* *If not, go to question 10*

4. How clear did you consider the personalized feedback/acknowledgement letter clear?
   - o Very clear
   - o Clear
   - o Neutral
   - o Unclear
   - o Very unclear

5. How useful did you consider the personalized feedback/acknowledgement letter useful?
   - o Very useful
   - o Useful
   - o Neutral
   - o Not useful
   - o Not useful at all

6. The personalized feedback/acknowledgement letter meets my expectations:
   - o Strongly agree
   - o Agree
   - o Neutral
   - o Disagree
   - o Strongly disagree

7. How satisfied are you about the personalized feedback/acknowledgement letter?
   - o Very satisfied
   - o Satisfied
   - o Neutral
   - o Unsatisfied
   - o Very unsatisfied

8. Did you discuss the personalized feedback/acknowledgement letter with your healthcare professional?*

9. Do you have any suggestions for improvement of the personalized feedback/acknowledgement letter?*

Your experiences with reporting

10. I made the report for: *myself/somebody else*

11. Did somebody help you to make the reports?*

12. Completing the reporting form was:
   - o Very easy
   - o Easy
   - o Neutral
   - o Difficult
   - o Very difficult

12. Would you report again if you would experience a possible adverse drug reactions?*

13. Would you encourage others to report possible adverse drug reactions?*

15. Do you have any suggestions for improvement of the reporting form?*

**Questions were answered by 'yes (namely…)', 'no' or 'I don't know'*

APPENDIX 2. NEW GENERAL ACKNOWLEDGEMENT LETTER FOR PATIENTS

Dear (name reporter),

Thank you for reporting to the Netherlands Pharmacovigilance Centre Lareb. By reporting adverse drug reactions you contribute to a safer use of medicines and vaccines.

You report has been registered under the number 12345 and will – anonymously – be included in the Lareb database. This is a database in which all adverse drug reaction reports of all drugs in the Netherlands are collected. Each adverse drug reaction report is assessed by an expert. In addition, reports are regularly discussed by a team of experts within Lareb. In this way, Lareb gets a good impression of the safety of medicines and will take action if necessary.

At this moment we have no further questions about your report. If we have any questions in the future, we will contact you.

If you have any further questions or other complaints, we advise you to contact your doctor or pharmacist. Should you experience other possible adverse drug reactions in the future we would be grateful if you could also report this to Lareb.

Thank you again for reporting.

Best regards,

6

General Discussion

PATIENT PARTICIPATION IN PHARMACOVIGILANCE

This thesis explored the impact of patient participation on pharmacovigilance. In recent years, there has been an increased interest in patients as reporters in pharmacovigilance. Several studies demonstrated that patients can have a positive contribution to pharmacovigilance. Nevertheless, many aspects of their contribution remained unclear. We aimed to identify the effect of patient participation on pharmacovigilance by exploring four main aspects, namely (i) information related to the nature of the reported adverse drug reaction (ADR), (ii) the quality of reported information, (iii) the contribution to signal detection, and (iv) practice of pharmacovigilance concerning feedback for patients. Figure 1 shows the place of the studies of this thesis in the circle of knowledge generation and practice of pharmacovigilance. ADRs experienced in daily practice can be reported to the pharmacovigilance centre. This generates knowledge about ADRs, and this knowledge is given back to healthcare professionals and patients. The studies described in the Chapters 2, 3 and 4, concern the information that is reported by patients and healthcare professionals. The study described in Chapter 5 provides new insights how to provide feedback to patient reporters.

In this concluding chapter the overall findings are discussed in a broader context. In addition, we come with some practical recommendations on how to strengthen the field of pharmacovigilance.

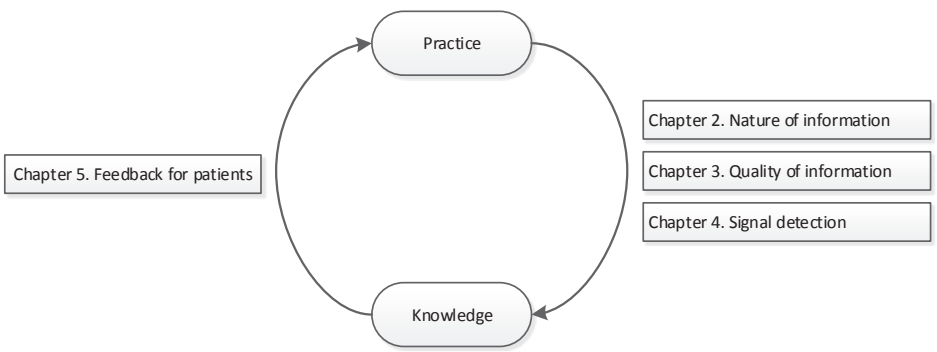

Figure 1. *Position of studies of this thesis in the circle of knowledge generation and practice of pharmacovigilance*

MAIN FINDINGS

Patients report useful information

In Chapter 2 we showed that patients report useful information about ADRs. In Chapter 2.1 we drafted a list of elements of information that were considered important concerning ADR reporting by different stakeholders in pharmacovigilance. This list was used in Chapter 2.2 to make an in-depth comparison between information in patient versus healthcare professional ADR reports. In general, the nature of information was comparable between both groups. Patient reports were however more focused on patient-related information and the impact of the reported ADR, whereas reports by healthcare professionals provided more clinically related information, like the patient's medical history and information related to the suspected drug.

In Chapter 2.3 we focussed on the impact of ADRs on the patient's health related quality of life (HR-QOL). Several studies demonstrated that patients bring a new dimension to pharmacovigilance by reporting about the impact of the ADR on their daily life. They are more likely than healthcare professionals to report about it [1-6] and they consider it to be an important topic [7]. Moreover, it was found to be one of the main motives for patients to report a possible ADR [8]. In chapter 2.3, we explored which domains of HR-QOL ADRs have most impact on. We found that ADRs reported by patients who experienced possible ADRs after the packaging change of the drug Thyrax®, had the highest impact for the domains 'daily activities', 'overall health status', and 'mental health', and the lowest for 'physical fitness'. In addition, we explored determinants for change in HR-QOL due to the ADR. The perceived severity of the ADR was found to be a determinant for all domains of HR-QOL. The patient's age, sex, educational level and absence from work due to an ADR were correlated to at least one domain.

Patients report high quality of information

Chapter 3 demonstrated that patients report high quality of information, this quality was comparable to that in healthcare professional reports. The latter group had however a higher quality for patient characteristics, for example risk factors and concomitant medication. This was in line with previous findings and may be explained by the fact that a question about the patient's medical history is not present on the patient reporting form.

Patient reports contribute to early detection of new signals

In the study described in Chapter 4 we focussed on time to signal detection. We showed that healthcare professionals generally reported earlier than patients. This

was the case for ADRs classified as IMEs as well as non-IMEs. Analysis of the individual signals demonstrated that the overall difference in time to reporting was small. Besides aspects of timing, this study showed that patients have a substantial quantitative contribution to signal detection in pharmacovigilance, mainly for signals classified as non-IMEs.

Practice of pharmacovigilance

As a final point of this thesis, we explored ways to give feedback to patient reporters. In Chapter 5 we showed that patients were satisfied with feedback from the pharmacovigilance centre in response to their reported ADR, whether this was a personalized feedback or a general acknowledgement letter. They find it clear, useful and it meets their expectations.

WHAT CAN WE LEARN FROM THESE FINDINGS?

More attention for identifying more details on known ADRs

Pharmacovigilance should undertake more efforts to identify more details of known ADRs and structure this information in a systematic way. Patients want and need comprehensive and accurate information about their drugs so that they can participate in decisions about their healthcare. In particular, they require information about the likely risks and benefits that are associated with the different treatment options [9]. Information about ADRs as presented in the Summary of Product Characteristics (SPC) or in textbooks usually only provides knowledge about the occurrence of ADRs. Information in terms of time course, management, risk factors and impact on the patient's daily life are often not described, even though this is important information for patients and healthcare professionals [10]. Although this type of information is present in pharmacovigilance databases, at the moment this information is not used to its full extent. We have learned that, like healthcare professionals, patients can contribute in providing information to identify new characteristics of ADRs. They give a detailed description of what happened and in addition to healthcare professionals, they are more likely to report about the impact of the ADR on their quality of life. The increase of the number of patient reports, mainly in Europe, indicates that patients are also willing to report [11].

New methodologies should be used to analyse the circumstances and clinical presentation of ADRs. For the detection of ADRs not described in the SPC, disproportionality analysis can be used as a first step of assessment. This does however not allow for the in-depth analysis of circumstances and clinical presentation of ADRs and the

specific circumstances under which they occur [10]. A case-by-case based analysis seems suitable, although this method is time-consuming. Due to this, it is wise to first prioritize the drug-ADR associations that are in need for such a description of circumstances and clinical presentation. From a pharmacovigilance centre perspective, this may for example be drug-ADR associations that are frequently reported. Involving patient or healthcare professional organisations may also be effective in order to find out what information about ADRs is needed in daily practice.

With the growing amount of unstructured information, the application of text mining is a potential option in order to make use of the richness of patient experiences, described in their reports [12]. With text mining, algorithms are being designed that look at specific text patterns, for example in clinical notes, comments from social media, or scientific literature. In recent years, this technique has been used increasingly in the field of biomedicine. It can be used to gather significant information on ADRs from different and heterogeneous textual sources, supporting researchers and clinicians with the challenging task of improving patient safety [13]. Within a pharmacovigilance centre, this technique may be used to search for specific patterns, for example about the impact of ADRs.

Besides the spontaneous reporting methods, we may also want to think about new methods to gain information about circumstances and clinical presentation of ADRs. Spontaneous reporting systems can be an important source for information about characteristics of ADRs. However, when a high number of reports is needed in order to identify characteristics of ADRs, other methods for data collection may be better suited. One example is cohort event monitoring, in which a group of patients, using a specific drug or experiencing a certain ADR, is followed over time, using for example electronic questionnaires. This method can be used in clinical practice and combines the strengths of the pharmaco-epidemiological as well as the clinical pharmacovigilance approach of drug safety surveillance [14]. In the Netherlands, Pharmacovigilance Centre Lareb has positive experiences with gaining information about circumstances and clinical presentation of ADRs, using the cohort event monitoring application 'Lareb Intensive Monitoring' (LIM). An example is the study about time course, outcome and management of ADRs associated with the drug metformin, which showed for instance that most ADRs recover spontaneously without withdrawal of metformin [15]. The LIM-system has been further developed to a flexible method in which answers given in a previous questionnaire can be automatically shown in the next questionnaire, including follow-up questions. In this way, the clinical presentation of ADRs and patient experiences can be followed over time in a patient friendly way.

Optimise reporting forms for specific groups of reporters

In order to capture all the relevant information that the specific types of reporters can provide it is important that pharmacovigilance centres optimise ADR reporting forms for patients and healthcare professionals [16]. There have been some concerns in the past that patients lack knowledge and skills to report the needed clinical information, and that the quality of reports coming from patients may be lower than reports made by healthcare professionals [17]. Even though structured reporting forms are being used, the type and quality of reported information depends on the reporter's skills. Due to this, spontaneous reporting systems are sensitive for variations in quality of reports and missing data [18]. The studies described in Chapter 2 and 3 about the nature and quality of information reported by patients compared to healthcare professionals indicate that these concerns seem unfounded. Patients and healthcare professionals report from their own perspective. Specific questions could be added to the reporting forms to trigger to provide this specific type of information. For example, for patients, specific questions could be added about a description of what happened and the impact of the ADR on their daily life.

Providing feedback to patients

Pharmacovigilance centres should focus more on feedback for patient reporters. Studies demonstrated that patients want to be informed after they reported a possible ADR to a pharmacovigilance centre [19-21]. Patients for example would like to know what will happened with their reports or they would like information about the ADR. Little is known about if and how pharmacovigilance centres provide feedback to patients. From our knowledge, only few countries send feedback to patients [19-21]. An eleven country survey on patient reporting demonstrated that New Zealand, Malaysia, Australia and the Netherlands send personalized feedback. Other included countries only send a letter of confirmation upon receiving the reports and/or information about what will happen with the report [19].

The study in Chapter 5 demonstrated that patients are satisfied with personalized feedback as well as with a general acknowledgement letter. We believe pharmacovigilance centres should make efforts to draft at least a general acknowledgement letter, explaining for example how their report is handled, privacy aspects concerning reported personal information, and what patients can expect from the pharmacovigilance centre. This would raise awareness about ADRs, spread knowledge about the work of a pharmacovigilance centre and makes that patients feel that their participation is appreciated.

CHANGES IN SPONTANEOUS REPORTING IN THE NETHERLANDS

Following the work presented in this thesis, a number of changes were made to the Dutch spontaneous reporting form. Efforts were made to make the patient ADR reporting form more user friendly. The focus was mostly on the wording and ordering of the questions. As described in Chapter 2, in the past, the patient reporting form had no specific question about the medical history. In the current form, such a question is provided in the form of a question that askes about possible other explanations for the occurrence of the ADR, including other diseases or allergies. Also, a question about the impact of the ADR, asked for each reported ADR, was added.

Based on the analysis in Chapter 2 we know that patients find the impact of ADRs an important topic and that they are willing to answer questions about the impact of the ADR on their daily life. In the past, this subject remained unexplored. We believe that more efforts should be made to collect this kind of information. For daily practices at the Dutch pharmacovigilance centre, meaning assessment of ADR reports and signal detection, information about of the impact of ADRs is preferred. Currently, Lareb is still exploring the wording of the question. Two formulations will be compared, namely (i) *What was the impact of the ADR on your quality of life* and (ii) *What was the severity of the ADR?* The answer option of both questions was a 5-point scale ranging from 'not at all' to 'very much', including an open text field in which patients could explain their given answer in their own words. Analysis of the first reports in which this question (i) was answered demonstrated that patients took the opportunity to explain in their own words how ADRs influenced their daily life. Aspects that were mostly mentioned were: the severity of the adverse drug reaction, impact on mood or concentration, overall (change in) health, physical impairment, and limitations in social activities. This is valuable information in order to understand the actual impact of ADRs. Moreover, it would enable healthcare professionals to provide detailed information on the consequences of these ADRs from a patient perspective [22]. It should however be noted that many reports may be needed to analyse and compare the impact of reported ADRs. Many different aspects in a patient's life may cause diversity in how patients experience an ADR [23]. Furthermore, it should be kept in mind that, due to the spontaneous approach, patients who spontaneously report an ADR may experience a bigger impact compared to those that do not report.

CONSIDERATIONS FOR USE OF DATA

For the studies described in this thesis we used reports of the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO Global database of individual

case safety reports, VigiBase [24]. Spontaneous reporting systems have the advantage of real life data, including facts and interpretations of the reporter. It is a relatively inexpensive method which can be used during the entire lifecycle of a drug, in the entire population [18,25]. Spontaneous reporting systems have some shortcomings. Underreporting is mostly mentioned as a major shortcoming of spontaneous reporting systems. Because these systems are not set up to calculate incidence rates, we believe underreporting is mainly a problem for ADRs that are not described in the SPC, and not so much for all ADRs that occur in daily practice. Missing data is probably a much bigger shortcoming of spontaneous reporting systems. Reporting varies with the reporters' skill and experience to detect the ADR, their level of understanding of the spontaneous reporting system, and their workload [18,25]. Missing data can however partly be solved by using structured reporting forms, including mandatory questions, and active following-up on missing information by the pharmacovigilance centre. Selection bias should be kept in mind when data, obtained by a spontaneous reporting system are used. People can have several motivations to report ADRs [8]. For example, when the impact of ADRs on the patient's daily life is explored, motivation of reporting can bias the results; patients with a high impact may be more likely to report their ADRs. In addition, it can be influenced by other factors, such as media attention [5,26].

For the studies described in this thesis, it is mainly of importance to mention that, in the Netherlands, the main method for reporting is by the electronic reporting form. For this, patients must (i) have skills to fill in the reporting form and (ii) have access to the internet. The study described in Chapter 5 as well as from another questionnaire study from Lareb [8] was demonstrated that the level of education of patients contributing to the study is higher compared to the general Dutch population. This may have introduced some selection bias. Concerning access to the internet, limited selection bias was expected. Statistics Netherlands reports that 94.4% of the Dutch households (at least one person between age 16 and 74) had Internet access in 2016. For people aged 25-45 years old this is 99.1% and for people aged of 65 this was 77.6% [27].

IMPLICATIONS FOR FUTURE STUDIES

Comparison of nature and quality of reported information between countries

For this thesis, we mainly focussed on Dutch reports. Concerning information in literature about information reported by patients, findings are mainly from the same European countries; the Netherlands, the UK and Denmark [28]. Generalization of these results should be done with caution since cultural aspects can be of influ-

ence. These can be patient as well as healthcare professional related, for example the patient's level of knowledge and healthcare professional's beliefs about the patient's skills, treating patients as equal partners in healthcare, attitude about reporting, and facilities or resources to make a report [29]. Other countries should be encouraged to analyse the nature and quality of the reported information by patients and healthcare professionals. If we are able to observe differences in quality, we could think of ways of how to improve the quality of reported information. In order to do so it is wise to develop methodologies that can internationally be used.

Healthcare professionals with different backgrounds

This thesis mainly focussed on information reported by patients versus healthcare professionals in general. In the study described in Chapter 2.2 we made a sub-analysis for healthcare professionals with different backgrounds; general practitioners, pharmacists and specialist doctors. Also here, there are differences in information that is being reported. For the future, it is important to also make a distinction between the several healthcare professional professions in order to also explore their strengths and weaknesses.

Development of new methods for structuring information

When pharmacovigilance centres decide to give more focus on identifying and structuring characteristics of known ADRs, new methodologies should be developed. Methods should be developed in such a way that they are internationally useable, with small adaptation. Also, more experience can be gained with data mining techniques. Unstructured information, for example about the impact of the ADR, may in this way be analysed.

AWARENESS AND EDUCATION

Raising public awareness of the existence and purpose of pharmacovigilance is vitally important to increase patient involvement [16]. The growing number of patient reports in Europe indicates patients' high motivation to report ADRs. A recent analysis on data of the European database EudraVigilance demonstrated an increase of patient reports in terms of numbers and in the proportion of patient reports compared with healthcare professional reports [30]. Studies in the UK and Netherlands however demonstrated that a large part of the general public is not aware of the possibility to report ADRs to the national pharmacovigilance centre; only 8.5% of the general adult population in the UK and 17% in the Netherlands is aware of it [31]. More attention for ADRs is also important since there are still high numbers of hospitalizations due

to ADRs. A recent update on a medication safety study in the Netherlands demonstrated that the number of drug-induced hospitalisations raised from 39,000 in 2008 to 49,000 in 2013. For patients aged over 65, about 48% of these hospitalisations were potentially avoidable. For patients aged under 65, this was about 25% [32]. Greater awareness of ADRs by patients and healthcare professionals may prevent unnecessary treatment, hospitalisation and suffering, and can therefore also prevent unnecessary costs [33].

Pharmacovigilance Centre Lareb is actively involved in training and education activities. In 2013, Lareb was designated the WHO Collaborating Centre for Pharmacovigilance in Education and Patient Reporting. Its role is to assist the WHO in training Member Countries on how to handle patient reports [34]. Lareb aims to serve as a platform for knowledge transfer by providing training, conducting research, and developing best practice for staff active in pharmacovigilance, both at national centres as well as in academia [35]. The first Lareb Conference on Patient Reporting was held in 2015. The meeting had 60 participants from 21 different countries. Several subjects relating patient reporting were discussed. Interviews with some of the participants indicated that this fulfilled their needs [36]. In addition, Lareb is increasingly working together with patient organisations. This provides valuable information about the use of medicinal drugs, and also gives the opportunity to share our knowledge with patients [37].

FINAL REMARKS

Studies described in this thesis demonstrated that patients add great value to pharmacovigilance. They report high quality and useful information about ADRs, and they bring a new dimension to pharmacovigilance by reporting about the impact of ADRs on their daily life. Patients and healthcare professionals both report from their own perspective. Information from both groups are complementary, and together they can provide a comprehensive description of the clinical presentation and circumstances of occurrence of ADRs. Concerning their contribution to signal detection, patients contributed a fair share of reports on ADRs that subsequently became new signals. We found no reason to believe they slow down the process of detection of new drug safety signals. Patients are actively involved in ADR reporting and they want to receive feedback from a pharmacovigilance centre in response to their reported ADR. They are satisfied with a personalized feedback as well as a general acknowledgement letter. The findings show that patients should be seen as equal partners, and for an optimal pharmacovigilance, both healthcare professionals and patients should be encouraged to report.

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Summary & Samenvatting

SUMMARY

In recent years, patient participation has become more important in pharmacovigilance (drug safety surveillance). The World Health Organization (WHO) defines pharmacovigilance as *the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems*. The primary aim of pharmacovigilance is the timely detection of new drug safety signals. Before drugs are marketed, they undergo extensive risk assessment. Nevertheless, new adverse drug reactions (ADRs) and relevant new information on known ADRs are detected when drugs are marketed and more widely used under more diverse conditions.

National pharmacovigilance centres and Marketing Authorization Holders (MAHs) monitor the safety of drugs by making use of so-called spontaneous reporting systems. Possible ADRs or other drug safety risks noticed in daily practice can spontaneously be reported to a pharmacovigilance centre or MAH by healthcare professionals and patients. Subsequently, pharmacovigilance centres and MAHs perform signal detection activities on the received reports. In addition, pharmacovigilance centres disseminate information about ADRs in order to increase knowledge and awareness about ADRs. All these activities aim to increase the safety of drugs used in daily practice.

The aim of this thesis is to explore the impact of patient participation on pharmacovigilance. Although the patient is the one who experiences the ADR and could for this reason report first-hand information, patient participation has not always been common. Initially, there were for example concerns about the quality of information reported by patients. In only a few countries patients were able to report ADRs directly to the national pharmacovigilance centre, among which the USA and Australia. Over the years there has been a change in attitude in which patient's experiences are valued. The 2000s saw a dozen countries implement patient reporting systems, with Denmark and the Netherlands being the first countries of the European Union (EU) in 2003. In the EU, the role of patients as stakeholders in pharmacovigilance became official after the implementation of the pharmacovigilance legislation (Regulation No 1235/2010) in July 2012. This legislation has enabled patients throughout the EU to report their drug concerns directly to the national pharmacovigilance centre.

The introduction of this thesis (**Chapter 1**) starts with a description of pharmacovigilance and the start of patient participation. Despite all positive experiences and efforts that have been made to explore how patients contribute to pharmacovigilance, there is still a gap in knowledge about the actual impact of direct patient reporting. This thesis focusses on four main topics: (i) information related to the nature of the

reported ADR; (ii) quality of reported information; (iii) contribution to signal detection; and (iv) practice of pharmacovigilance in terms of feedback for patients.

The studies in **Chapter 2** assess the nature of information reported by patients compared to that reported by healthcare professionals. **Chapter 2.1** studies what reporters and assessors of ADRs consider important information regarding an ADR report. For this purpose a total of 16 patients, healthcare professionals and ADR assessors were interviewed. Patients mentioned that the severity of the ADRs and the impact on their daily life were important subjects. For healthcare professionals, either reporters or assessors, the focus was mainly on topics relating to causality assessment. From all items mentioned, a list of 56 items was drafted.

Subsequently, the study in **Chapter 2.2** aims to explore the differences in reported information between patient and healthcare profession ADR reports. Using the previously drafted list, 200 reports of patients and healthcare professionals were compared. Patients reported the impact of the ADR and the patient's weight and height more frequently than healthcare professionals, the differences being statistically significant. Healthcare professionals, on the other hand, reported the route of administration of the drug and the medical history statistically significantly more frequently. Although not statistically significant, it is worth mentioning that patients were more likely than healthcare professionals to report the outcome of the ADR, a detailed description of what happened, the severity, contact with or between healthcare professionals and the patient's thoughts about causality. Healthcare professionals were more likely than patients to report about items related to the drug use: drug dosage, the pharmaceutical forms of the drug, and other suspected medication. This study concluded that patient reports are more focussed on patient related information and the impact of ADRs, whereas reports from healthcare professionals provide more clinically related information.

Chapter 2.3 studies the impact of ADRs on the patient's health related quality of life (HR-QOL). Several studies demonstrated that patients bring a new dimension to pharmacovigilance by reporting information about the impact of the ADR on their daily life. There are several domains of HR-QOL on which ADRs can have an influence, for example physical or social aspects. From a pharmacovigilance perspective, capturing and making the best use of this information remains a challenge. For this study a specific group of reporters was used; they all reported an ADR in relation to a change in package of the drug Thyrax® (levothyroxine). Five domains of HR-QOL were explored: physical, social, mental, daily activities and overall health status. In total, 1167 patients were included for this study. It was demonstrated that experiencing possible ADRs after the packaging change of the drug Thyrax® statistically significantly decreased the HR-QOL score for all explored domains. The experienced

ADRs had the highest impact on the domains daily activities, overall health status, and mental health, and the lowest for physical fitness. In addition, determinants for change in HR-QOL due to the ADR were explored. The perceived severity of the ADR was found to be a determinant for all domains of HR-QOL. It was suggested that pharmacovigilance centres could add a question about the severity of the ADR to the patient reporting form in order to gain information about the impact of ADRs on the patient's HR-QOL.

Chapter 3 compares the level of clinical information reported by patients and healthcare professionals. Clinical information is needed to assess the causal relationship between a drug and an ADR in a reliable way. Little is known about the level of relevant clinical information reported by patients. For this study, reports on the same case were used, meaning cases with a report from both the patient and the healthcare professional. The extent to which relevant clinical information was reported was assessed by trained pharmacovigilance assessors, using a structured tool that categorizes the level of clinical quality of reports into poorly, moderately or well documented. A total of 197 cases were included. In 107 cases, patients and healthcare professionals reported a similar level of clinical information. For 79 cases reports differed by only one category (well vs. moderately or moderately vs. poorly). Of those, for 34 the patient had a higher score and for 45 the healthcare professional had a higher scored. This study found no statistically significant differences in the level of reported clinical information between reports from patients and healthcare professionals. It was concluded that patients reports clinical information at a similar level as their healthcare professional.

Chapter 4 studies the contribution of patient reporting to early signal detection by exploring if there is a difference between patients and healthcare professionals in time to reporting drug-ADR associations for reports which contributed to drug safety signals. Little is known about the extent to which patient reporting might impact timely signal detection and whether this is different for ADRs classified as so called 'important medical events' (IMEs) compared to non-IMEs. For this study, ADR reports were selected from the WHO Global database of individual case safety reports, VigiBase, based on drug-ADR associations described in 60 drug safety signals detected by Lareb between 2011 and 2015. These were 18 IMEs and 42 non-IMEs. A total of 2822 reports were included, of which 52.7% were patient reports. The proportion of patient reports in the individual signals ranged from 0% to 84.4%, with a median of 25.0%. The 18 IMEs signals included 556 reports (31.5% patient reports) and the 42 non-IMEs signals included 2266 reports (57.9% patient reports). Overall, healthcare professionals reported earlier than patients: median 7.0 vs. 8.3 years, the difference

being statistically significant. Similar results were found for IMEs: healthcare professionals' versus patients' median time to reporting was 6.9 vs. 8.1 years and for non-IMEs 7.0 vs. 8.2 years. This study concluded that patients contributed a large proportion of reports on drug-ADR pairs that eventually become drug safety signals. This corroborates earlier findings on the contribution of patient reports to signal detection in pharmacovigilance. For all signals, median time to signal detection was 10.4 years. Healthcare professionals generally reported 1.3 year earlier than patients. This was the case for ADRs classified as IMEs as well as non-IMEs. This highlights an opportunity to further increase the value of patient reporting in the future, by encouraging patients to report suspected ADRs earlier.

The study in **Chapter 5** explores the satisfaction of patients towards personalized and general feedback from the pharmacovigilance centre in response to their reported ADR. Besides collecting information about ADRs, pharmacovigilance centres disseminate information about ADRs in order to increase the attention for and knowledge about ADRs. A method of providing information is by sending feedback in response to the reported ADR. This feedback can for example contain general information about what the pharmacovigilance centre will do with the report. It can also be more personal by containing feedback on the drug-ADR association the patient reported on. For this study, patient reporters who for the first time reported an ADR to the Netherlands Pharmacovigilance Centre Lareb received either a personalized or a general acknowledgement letter. A web-based questionnaire was used to explore their satisfaction. A total of 245 patients responded; 123 in the personalized letter-group and 122 in the general feedback-group. Responders of both groups were satisfied with the received feedback. Statistical analysis demonstrated that respondents of the personalized feedback-group were however more satisfied and considered the feedback more clear and useful compared to respondents of the acknowledgement letter-group This study concluded that patients are satisfied with feedback from a pharmacovigilance centre, whether this is a personalized feedback or a general acknowledgement letter. They find it clear, useful and it meets their expectation. Although differences were found between the two types of feedback, these differences did not indicate dissatisfaction towards the received feedback.

Chapter 6 is a general discussion which focusses on what we can learn from the findings of this thesis and implications for future studies. The main learning points are that there needs to be more attention for identifying further details of known ADRs; that we need to optimise reporting forms in order to capture all the relevant information that specific types of reports can provide; and that pharmacovigilance centres need to provide feedback to patients in response to their reported ADRs. For

the future it is suggested that there needs to be a comparison of the nature and quality of reported information between countries; there should be focus on differences in reported information between healthcare professionals with different backgrounds; and new methods for structuring information should be developed.

This thesis concludes that patient reporting adds great value to pharmacovigilance. Patients should be seen as equal partners, and for an optimal pharmacovigilance, both healthcare professionals and patients should be encouraged to report.

SAMENVATTING

Patiëntenparticipatie is de afgelopen jaren steeds belangrijker geworden in farmacovigilantie (geneesmiddelbewaking). De Wereldgezondheidsorganisatie definieert farmacovigilantie als *de wetenschap en activiteiten met betrekking tot de opsporing, beoordeling, kennis en preventie van mogelijke bijwerkingen of andere geneesmiddel-gerelateerde problemen*. Farmacovigilantie heeft als belangrijkste doel het tijdig herkennen van mogelijke veiligheidsrisico's van geneesmiddelen. Voordat een geneesmiddel op de markt komt wordt de veiligheid goed onderzocht. Toch is het niet uit te sluiten dat nieuwe bijwerkingen aan het licht komen wanneer een geneesmiddel op de markt komt en door een grote groep patiënten wordt gebruikt onder gevarieerde omstandigheden.

Nationale bijwerkingencentra en de producenten van geneesmiddelen bewaken de veiligheid van geneesmiddelen met behulp van een zogenoemd spontaan rapportage systeem. Mogelijke bijwerkingen of andere geneesmiddelveiligheidsproblemen kunnen vrijwillig gemeld worden aan een bijwerkingencentrum of aan de producent van het geneesmiddel door zorgverleners en patiënten. Bijwerkingencentra en de producenten van geneesmiddelen voeren signaaldetectie activiteiten uit op de ontvangen meldingen. Daarnaast verspreidt een bijwerkingencentrum informatie over bijwerkingen om de alertheid en kennis over bijwerkingen te vergroten. Al deze activiteiten samen hebben als doel het gebruik van geneesmiddelen in de dagelijkse praktijk veiliger te maken.

Het doel van dit proefschrift is om de impact van patiëntenparticipatie aan farmacovigilantie te onderzoeken. De patiënt is degene die de bijwerking ervaart en zou daarom een goede beschrijving van de bijwerking kunnen geven. Toch was het melden van bijwerkingen door patiënten niet altijd vanzelfsprekend. Er waren in eerste instantie bijvoorbeeld zorgen over de kwaliteit van informatie gemeld door patiënten. In het verleden hadden patiënten in slechts een aantal landen de mogelijkheid zelfstandig bijwerkingen te melden, voorbeelden hiervan zijn Amerika en Australië. Vanaf het begin van de 21^{e} eeuw gingen steeds meer landen meldingen van patiënten accepteren, waarvan Denemarken en Nederland in 2003 de eerste landen binnen de Europese Unie. In 2012 was er een doorbraak in de acceptatie van patiëntenparticipatie toen een nieuwe Europese farmacovigilantie wetgeving het mogelijk maakte voor patiënten in alle lidstaten van de Europese Unie om bijwerkingen rechtstreeks te melden aan het nationale bijwerkingencentrum. Patiënten kregen hierdoor een permanente rol in de bewaking van de veiligheid van geneesmiddelen.

De introductie van dit proefschrift (**hoofdstuk 1**) begint met een korte inleiding over farmacovigilantie en de start van patiëntenparticipatie. Vervolgens wordt ingegaan

op wat er in de literatuur inmiddels bekend is over informatie gemeld door patienten en de bijdrage ervan aan signaaldetectie. Ondanks alle positieve ervaringen met patiëntmeldingen en de inspanningen die zijn gedaan om te onderzoeken hoe patiëntmeldingen bijdragen aan farmacovigilantie, blijft er onduidelijkheid over de specifieke impact van patiëntmeldingen. Dit proefschrift focust zich op vier hoofdpunten, namelijk: (i) informatie gerelateerd aan de aard van de gemelde bijwerking, (ii) de kwaliteit van gemelde informatie, (iii) de bijdrage aan signaaldetectie en (iv) omgaan met patiëntmeldingen in de praktijk waarbij de focus ligt op informatie teruggeven aan patiënten.

De onderzoeken in **Hoofdstuk 2** gaan over de aard van informatie over bijwerkingen gemeld door patiënten vergeleken met die van zorgverleners. **Hoofdstuk 2.1** onderzoekt welke informatie belangrijk is wanneer we spreken over het melden van bijwerkingen. Om antwoord te geven op deze vraag zijn 16 melders (patiënten en zorgverleners) en beoordelaars van bijwerkingen geïnterviewd. Patiënten gaven aan dat zij de hevigheid van de bijwerkingen en de impact die het heeft op het dagelijks leven belangrijk vinden. Voor zorgverleners, zowel melders als beoordelaars, lag de focus meer op informatie waarmee de oorzakelijke relatie tussen het geneesmiddel en de bijwerking opgehelderd kan worden. Van alle onderwerpen die uit dit onderzoek naar boven zijn gekomen is een lijst gemaakt van 56 items.

De studie in **Hoofdstuk 2.2** onderzoekt wat de verschillen zijn in type informatie gemeld door patiënten en zorgverleners. Gebruikmakend van de eerder genoemde lijst zijn 200 meldingen van patiënten en zorgverleners met elkaar vergeleken. De impact van de bijwerking en de lengte en het gewicht van de patiënt zijn vaker door patiënten gemeld dan door zorgverleners, dit verschil is statistisch significant. De toedieningsroute van het geneesmiddel en medische voorgeschiedenis van de patiënt zijn vaker gemeld door zorgverleners dan patiënten, dit verschil was statistisch significant. Er zijn een aantal items die de moeite waard zijn om te vermelden, ondanks dat er geen statistisch verschil is gevonden tussen beide groepen. Patiënten melden vaker over de afloop van de bijwerking, ze geven een gedetailleerde beschrijving van wat er is gebeurd, de hevigheid ervan, contact met of tussen zorgverleners en zijn/haar gedachten over causaliteit. Zorgverleners melden vaker geneesmiddel gerelateerde items: de farmaceutische formulering van het geneesmiddel en andere verdachte geneesmiddelen. Deze studie concludeert dat er bij patiëntmeldingen meer focus lag op patiënt-gerelateerde informatie en de impact van de bijwerking terwijl bij meldingen van zorgverleners er meer focus lag op klinische informatie.

Hoofdstuk 2.3 gaat in op de impact van bijwerkingen op de kwaliteit van leven van patiënten. Uit vorige onderzoeken is gebleken dat patiënten vaker dan zorgverleners melden over de impact van de bijwerking op de kwaliteit van leven. Er zijn

verschillende domeinen van de kwaliteit van leven die door bijwerkingen beïnvloed kunnen worden, bijvoorbeeld lichamelijke en sociale aspecten. Vanuit het perspectief van farmacovigilantie is hier echter weinig over bekend. Voor dit onderzoek is een specifieke groep patiënten gebruikt; allen hebben een bijwerking gemeld in relatie met een verpakkingswijziging van het geneesmiddel Thyrax® (levothyroxine). Vijf domeinen van kwaliteit van leven zijn onderzocht: lichamelijk, sociaal, mentaal, dagelijkse activiteiten en algemene gezondheidsstatus. Deze studie laat zien dat de ervaren bijwerkingen een belangrijke vermindering gaven van de kwaliteit van leven voor alle onderzochte domeinen. De impact was het grootst voor de domeinen mentaal, dagelijkste activiteiten en de algemene gezondheidsstatus en het laagst voor lichamelijk activiteiten. Het was verder opvallend dat er een sterke relatie was tussen de ervaren hevigheid van de bijwerking en de vermindering van de kwaliteit van leven; hoe heviger de patiënt de bijwerking ervoer, hoe meer invloed dit had op de domeinen van kwaliteit van leven. Vanuit deze resultaten is voorgesteld dat bijwerkingencentra een vraag over de hevigheid van de bijwerking op het patiënten meldformulier toevoegen. Op deze manier kan een algemeen beeld gevormd worden van de impact van de bijwerking op de kwaliteit van leven van de patiënt.

Het onderzoek in **Hoofdstuk 3** vergelijkt de mate waarin klinische informatie is gemeld door patiënten vergeleken met zorgverleners. Klinische informatie is belangrijk om op een betrouwbare manier te kunnen beoordelen of er een oorzakelijk verband is tussen het gebruik van het geneesmiddel en de ervaren bijwerking. Er is nog weinig bekend over de mate waarin patiënten klinische informatie melden. Voor dit onderzoek is gebruik gemaakt van zogenoemde 'dubbelmeldingen'; meldingen die gedaan zijn door de patiënt en de zorgverlener van de patiënt. De mate waarin relevante klinische informatie is gemeld, is beoordeeld door ervaren farmacovigilantie beoordelaars met behulp van een gestructureerde methode. De klinische kwaliteit van de meldingen werd gecategoriseerd in slecht, matig of goed. In totaal zijn 197 dubbelmeldingen geïncludeerd. Voor 107 dubbelmeldingen was de kwaliteit van klinische informatie gelijk voor de melding van de patiënt en die van de zorgverlener. Voor 79 dubbelmeldingen was er een verschil van één categorie (goed versus matig of matig versus slecht). Voor 34 van deze dubbelmeldingen had de patiënt een hogere score en voor 45 de zorgverlener. Er is in dit onderzoek geen statistisch significant verschil gevonden in de mate waarin klinische informatie is gemeld door patiënten en zorgverleners. Deze studie concludeert dat de mate waarin patiënten klinische informatie melden vergelijkbaar is met zorgverleners.

Hoofdstuk 4 onderzoekt de bijdrage van patiëntmeldingen aan snellere signaaldetectie. Dit wordt gedaan door een vergelijking te maken van de snelheid van melden van

bijwerkingen die later bijdragen aan een nieuw signaal tussen patiënten en zorgverleners. Er is nog weinig bekend over de mate waarin patiëntmeldingen bijdrage aan snellere signaaldetectie en of dit verschillend is voor bijwerkingen die geclassificeerd zijn als zogenoemde 'belangrijke medische events' (BME) ten opzichte van niet-BME. Voor dit onderzoek zijn meldingen geselecteerd uit de internationale database van de Wereldgezondheidsorganisatie, VigiBase, op basis van geneesmiddel-bijwerking associaties beschreven in 60 signalen gedetecteerd door Lareb tussen 2011 en 2015. Dit betrof 18 BME en 42 niet-BME. In totaal zijn 2822 meldingen geïncludeerd, waarvan 52,7% patiëntmeldingen. De hoeveelheid patiëntmeldingen in de individuele signalen varieerde van 0% tot 84,4%. In totaal waren er 556 meldingen van bijwerkingen geclassificeerd als BME (31,5% patiëntmeldingen) en 2266 meldingen een niet-BME (57,9% patiëntmeldingen). Over het algemeen meldden zorgverleners sneller dan patiënten, met een mediane tijd van 7,0 versus 8,3 jaar. Dit verschil was statistisch significant. Vergelijkbare resultaten werden gezien voor de analyse naar bijwerkingen geclassificeerd als BME: mediane tijd tot melden door zorgverleners en patiënten was respectievelijk 6,9 versus 8,1 jaar en voor de niet-BME 7,0 versus 8,2 jaar. Deze studie concludeert dat patiënten een groot aandeel hebben in meldingen die later hebben bijgedragen aan een nieuw signaal. Dit komt overeen met resultaten van eerdere studies naar de bijdrage van patiëntmeldingen aan signaaldetectie. Voor alle signalen samen genomen was de mediane tijd tot aan signaaldetectie 10,4 jaar. Zorgverleners meldden 1,3 jaar sneller dan patiënten. Dit was het geval voor meldingen geclassificeerd als BME en niet-BME. Dit benadrukt de mogelijkheid om de waarde van patiëntmeldingen in de toekomst te vergroten door patiënten aan te moedigen vermoedelijke bijwerkingen eerder te melden.

Het onderzoek in **Hoofdstuk 5** onderzoekt hoe tevreden patiënten zijn met een persoonlijke reactie in vergelijking met een standaard bedankbrief met algemene uitleg. Naast het verzamelen van informatie over bijwerkingen wil een bijwerkingencentrum de aandacht voor en kennis over bijwerkingen vergroten. Dit kan bijvoorbeeld door een reactie te geven aan patiënten nadat zij een melding hebben gedaan. Dit kan een algemene reactie zijn waarin onder andere wordt uitgelegd wat het bijwerkingencentrum met de melding zal doen. Het kan ook een persoonlijke reactie zijn waarbij informatie wordt gegeven over de specifieke geneesmiddel-bijwerking associatie waarover de patiënt heeft gemeld. Voor dit onderzoek werden patiënten die voor de eerste keer een melding deden aan Nederlands Bijwerkingencentrum Lareb in twee groepen verdeeld: de eerste groep kreeg een persoonlijke reactie, de tweede groep een standaard bedankbrief. Vervolgens is een online vragenlijst gebruikt om patiënten te vragen naar de tevredenheid. In totaal hebben 245 patiënten meegedaan aan dit onderzoek; 123 in de persoonlijke reactie-groep en 122 in de bedankbrief-

groep. Beide groepen waren tevreden met de reactie die zij hebben ontvangen. De groep die de persoonlijke reactie ontving was echter meer tevreden en zij vonden de reactie duidelijker en bruikbaarder dan de patiënten die een standaard bedankbrief hebben ontvangen. Dit verschil was statistisch significant. Dit onderzoek concludeert dat patiënten tevreden zijn met beide vormen van feedback. Ze vinden de reactie nuttig, duidelijk en het voldoet aan de verwachtingen die zij hadden. Ondanks dat er verschillen zijn gevonden in tevredenheid tussen beide groepen, is er geen reden te geloven dat deze patiënten ontevreden zijn met de ontvangen reactie.

Hoofdstuk 6 is een algemene discussie die zich focust op wat we kunnen leren van de bevindingen van dit proefschrift en suggesties voor toekomstig onderzoek. De belangrijkste leerpunten zijn dat er meer aandacht moet komen om karakteristieken van bijwerkingen beter in kaart te brengen; meldformulieren moeten worden geoptimaliseerd zodat specifieke type melders alle relevante informatie waarover zij beschikken kunnen melden en bijwerkingencentra zouden een reactie moeten sturen aan patiënten die een bijwerking hebben gemeld.

Voor toekomstige studies is voorgesteld dat er een vergelijking zou moeten komen van de kwaliteit van gemelde informatie tussen verschillende landen; er moet meer aandacht zijn voor verschillen in informatie gemeld door verschillende type zorgverleners en er zijn aanvullende methoden nodig om informatie over bijwerkingen beter te kunnen structureren.

Dit proefschrift concludeert dat patiëntmeldingen van grote waarde zijn voor farmacovigilantie. Patiënten kunnen worden gezien als gelijkwaardige partners in farmacovigilantie en voor een optimale farmacovigilantie zouden zorgverleners en patiënten gestimuleerd moeten worden om te melden.

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Bijna 7 jaar geleden zat ik in de bus onderweg naar een sollicitatiegesprek bij het Nederlands Bijwerkingencentrum Lareb. Ik was net afgestudeerd en wist niet precies wat ik wilde doen qua werk. Wil ik het ziekenhuis in of toch liever onderzoek? De bus had vertraging, de trein naar Den Bosch ging ik waarschijnlijk niet halen. Ik belde mijn moeder: 'Zal ik een trein later nemen of maar gewoon terug gaan naar huis? Ik weet ook niet of dit echt iets voor mij is.'

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Articles marked with an asterix (*) relate to the work described in this thesis.

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