Patient participation in pharmacovigilance

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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 α = α/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$^\#$	97 (1.00$^\#$)	97 (0.75)	97 (1.00$^\#$)
Time to onset	95	96	1.00$^\#$	91 (1.00$^\#$)	97 (0.62)	97 (1.00$^\#$)
Outcome ADR**	91	81	0.04	85 (0.32$^\#$)	68 (0.01)	91 (0.99$^\#$)
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$^\#$)	12 (1.00$^\#$)	9 (0.76$^\#$)
No ADR after use of a similar drug	7	1	0.07$^\#$	3 (0.67$^\#$)	0 (0.19$^\#$)	0 (0.19$^\#$)
Other aspects that could have caused the ADR**	15	14	0.84	12 (0.78$^\#$)	12 (0.71$^\#$)	18 (0.66)
Seriousness**	**10**	25	0.01	12 (0.75)	21 (0.14$^\#$)	**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$^\#$)	3 (1.00)	9 (0.41$^\#$)
Dechallenge	10	12	0.65	9 (1.00$^\#$)	21 (0.14$^\#$)	6 (0.73$^\#$)
Rechallenge	9	3	0.07	3 (0.45$^\#$)	3 (0.51$^\#$)	3 (0.45$^\#$)
Recurrence	5	5	1.00	9 (0.41$^\#$)	0 (0.39$^\#$)	6 (1.00$^\#$)
Recovery date**	0	4	0.12$^\#$	3 (0.25$^\#$)	3 (0.25$^\#$)	6 (0.06$^\#$)
Time to recover	4	8	0.23	6 (0.64$^\#$))	6 (0.64$^\#$)	12 (0.11$^\#$)
Impact of the ADR on the patient's daily life	**17**	**2**	**<0.001**	0 (0.07$^\#$)	3 (0.29$^\#$)	3 (0.29$^\#$)
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$^\#$	3 (1.00)	9 (1.00$^\#$)	3 (1.00$^\#$)
Start date drug**	98	100	0.50$^\#$	100 (1.00$^\#$)	100 (1.00)	100 (1.00$^\#$)
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$^\#$)
Actions after occurrence of ADR	94	95	0.76	94 (0.99$^\#$)	97 (0.49$^\#$)	94 (0.99$^\#$)
Other suspect drugs*	4	14	0.01	12 (0.11$^\#$)	9 (0.37$^\#$)	21 (0.01$^\#$)
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	-

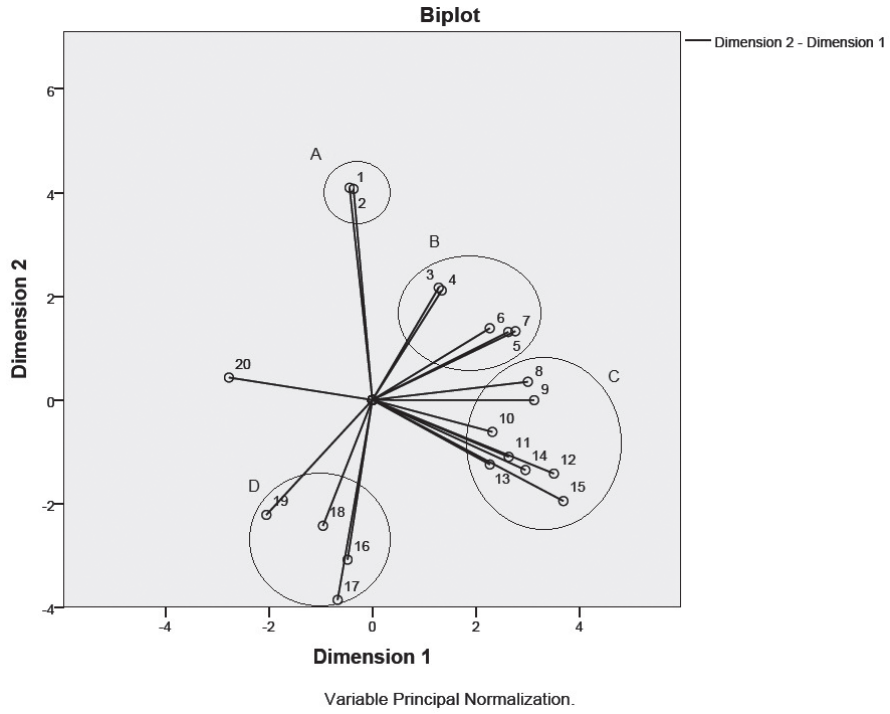

Figure 1. *Categorical principal components analysis*

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

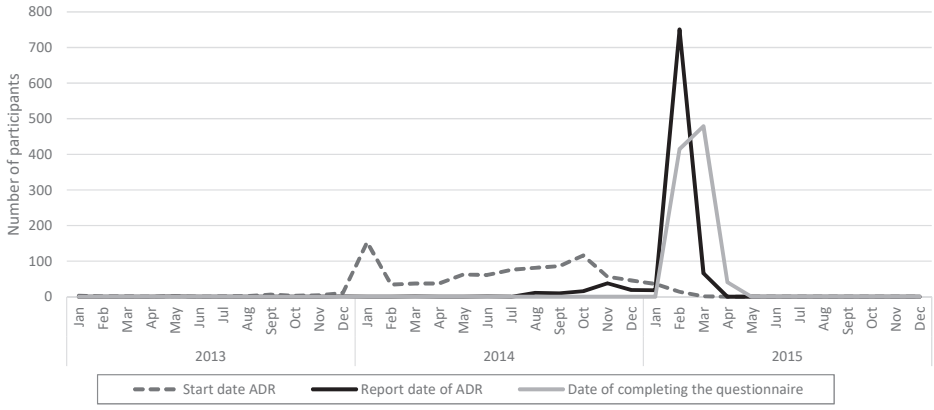

Figure 1. *Time lag between start date of the ADR, date of reporting and completing the questionnaire*

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	

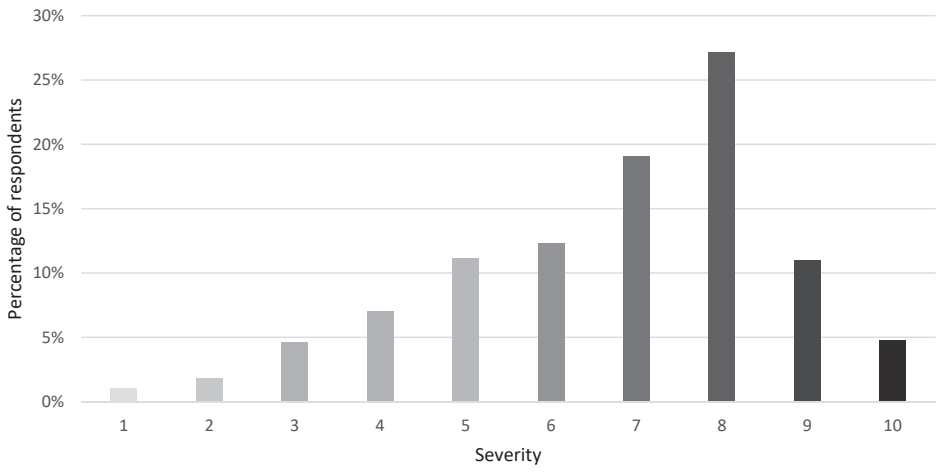

Figure 2. *Severity of the experienced adverse drug reactions*
Severity of the adverse drug reaction on a scale from 1 (no severity) to 10 (high severity) as experienced by patients

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