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ORIGINAL RESEARCH ARTICLE

Evaluation of Potentially Drug-Related Patient-Reported Common Symptoms Assessed During Clinical Medication Reviews: A Cross-Sectional Observational Study

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Abstract

Introduction Healthcare professionals tend to consider common non-alarming drug-related symptoms to be of little clinical relevance. However, such symptoms can have a substantial impact on the individual patient. Insight into patient-reported symptoms could aid pharmacists to identify improvements in medication treatment, for instance in the patient interview at the start of a clinical medication review (CMR).

Objective The objectives of this study were to describe the numbers and types of patient-reported symptoms assessed during a CMR and to elucidate their potential association with the drugs in use.

Methods This observational study was performed using data from a clinical trial on patient-reported outcomes of CMRs. Patients taking at least five drugs and who were eligible for a CMR were selected by 15 community pharmacies. Patients were asked to fill in a structured instrument, the Patient Reported Outcome Measure, Inquiry into Side Effects (PROMISE). Among other domains, this instrument offers a list of 22 symptom categories to report symptoms and their relationship with the drugs in use. The results of the PROMISE instrument together with information on patients' actual drug use were available for analysis. Besides descriptive analysis, associations with side effects as listed in the summary of product characteristics (SPC) of the drugs in use were assessed with logistic regression analysis.

Results Of the 180 patients included, 168 patients (93.3%) reported at least one symptom via the PROMISE instrument, which could be discussed with the pharmacist during the patient interview. In total, the patients reported 1102 symptoms in 22 symptom categories. Of these patients, 101 (56.1%) assumed that at one or more of the symptoms experienced were related to the drugs in use and 107 (59.4%) reported at least one symptom that corresponded to a 'very common' side effect listed in the SPC of a drug in use. Each additional drug in use with a specific symptom listed as a 'very common' side effect in its SPC statistically significantly increased the probability of a patient reporting the symptoms of 'dry mouth/thirst, mouth complaints', 'constipation', 'diarrhoea' and 'sweating'.

Conclusion Many patient-reported symptoms and symptoms potentially related to drugs in use were identified by administering the PROMISE instrument to users of at least five drugs being taking long-term. This information can be used in CMRs to improve patients' drug therapy.

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Key Points

Nearly all users with at least five drugs in long-term use reported at least one common symptom at the start of a clinical medication review.

More than half of the patients considered at least one drug in use to be responsible for a symptom experienced.

Concomitant use of drugs with the same side effect as listed in their summary of product characteristics increased the risk to patients reporting the corresponding symptoms of 'constipation', 'diarrhoea', 'dry mouth/thirst, mouth complaints' and 'sweating'.

1 Introduction

Symptoms are subjective signs of a disease or of a patient's condition [1] and may be caused by drugs being taken by a patient. Studies have shown that healthcare professionals tend to ignore non-alarming drug-related symptoms [2–4]. Instead, they mainly focus on (potentially) serious drug-related symptoms to prevent major harm to their patients [5–8]. In order to prevent these major harms, recommendations have been developed [9] and pharmacist-initiated interventions to avoid potentially preventable hospital admissions have been proposed [10]. As a consequence, less attention is paid to the reduction of common non-alarming symptoms in medication users.

Even when drug-related symptoms are non-alarming, they can still have a substantial impact on a subject's daily life. For instance, dizziness may increase the fear and risk of falling, muscle pain may reduce physical activity, and diarrhoea may induce or worsen social isolation. This may also lead to poor adherence or discontinuation of the drugs in use. Common non-alarming drug-related symptoms are less likely to be considered preventable than serious drug-related symptoms [11, 12]. Therefore, effective intervention strategies for the detection and amelioration of common drug-related symptoms are important to increase quality of life.

Patients taking multiple drugs in long-term use are more susceptible to adverse effects of drugs [13]. Consequently, amelioration of patient-experienced adverse effects should be a prominent part of a clinical medication review (CMR), aimed at optimising drug effectiveness and safety in patients with at least five drugs in long-term use. In The Netherlands, CMRs are performed by pharmacists in cooperation with general practitioners (GPs) according to the Dutch guidelines for CMRs [14, 15]. These guidelines distinguish six steps: patient selection, a patient interview, a medication analysis, a pharmaceutical care plan, implementation of recommendations, and a follow-up evaluation 3 months later. During the patient interview at the start of the CMR, patient-reported symptoms should be taken into account to prioritise further adjustment of the drug regimen [16–18]. As patients may fail to spontaneously report common drug-related symptoms, a self-report instrument may be helpful to detect potential drug-related symptoms [19].

While patients may not recognise all drug-related symptoms as such, awareness may be increased by asking about any experienced symptoms. In a cross-sectional study in the general Norwegian population (between 15 and 84 years), 96% of subjects reported subjective health complaints [20]. Hence, it may be expected that nearly all patients qualifying for a CMR will report one or more symptoms that may or may not be related to their drugs in use. By using an instrument to identify symptoms in advance, during the patient interview at the start of a CMR the pharmacist can focus on the evaluation and possible amelioration of these symptoms, especially when they appear to be drug related. The side effects of a drug are listed in its summary of product characteristics (SPC) by frequency of occurrence. Hence, SPCs are regularly consulted to assess whether symptoms are potentially drug related [14, 21]. The aims of the present study were to describe the numbers and types of patient-reported symptoms assessed during a CMR and to elucidate an association between these symptoms and a patient's drugs in use as indicated by the patient or when compared with the side effects listed in the SPCs of these drugs.

2 Methods

2.1 Study Design

The data for this cross-sectional observational study were collected within the context of a randomised clinical trial on the effect of pharmacists' interventions to reduce patient-reported drug-related symptoms in CMRs. In this trial (registered as number 4895 in the Netherlands Trial Register; http://www.trialregister.nl), after providing informed consent patients were randomised into an intervention group and a control group (unpublished data). All patients were invited to fill in a paper instrument, the Patient Reported Outcome Measure, Inquiry into Side Effects (PROMISE) twice: first, at the beginning of the study about 2 weeks before the patient interviews in the intervention group and, second, before the evaluation of treatment changes 3 months later. For this study, only the PROMISE data from the first measurement were used. The Arnhem-Nijmegen ethical committee determined that

ethical approval for the trial was not mandatory (registration number 2014/320).

2.2 Setting and Participants

2.2.1 Clinical Medication Review

In a CMR, drug therapy-related problems (DTPs) can be identified by judging the appropriateness of the drugs in use in combination with patient characteristics and laboratory values, as well as by interviewing patients in relation to problems regarding their drug use. The patient interview at the start of a CMR enables the pharmacist to focus on DTPs relevant from a patient perspective, such as drug-related symptoms [16–18]. In the trial mentioned in Sect. 2.1, input for these DTPs was provided by administering the PROMISE instrument.

2.2.2 Patient Reported Outcome Measure, Inquiry into Side Effects (PROMISE)

PROMISE is a concise instrument used to collect information on proper medication use that was developed to be used in the trial outlined in Sect. 2.1. It comprises five predefined domains: health status, beliefs and concerns about medicines, self-efficacy in understanding and using medicines, medication adherence, and potentially drug-related symptoms. Additionally, an open-ended question enables the patient to propose any issues to be discussed during the interview with the pharmacist. The first four domains were derived from existing instruments [22–25]. For the fifth domain, an item list of common symptoms was chosen to be used as such a list has been proven to be more sensitive to complete reporting than open-ended questions [26]. The item list should fit in the concise design of the PROMISE instrument and contain symptoms relevant for use in a CMR. For this reason a standardised list of specific symptoms was developed based on the most common side effects of drugs most frequently used in The Netherlands. To this end, information on volumes of drug use in The Netherlands was retrieved from the health insurance database (GIP [Genees-en hulpmiddelen Informatie Project] database) and the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen [SFK]) [27, 28]. The top 100 drugs were chosen from the GIP database as those with the most defined daily doses and were complemented with two drugs (amoxicillin, doxycycline) from the top 100 users [27]. As the GIP database only included reimbursed drugs, the list was complemented with two drugs (oxazepam, sildefanil) from the top five non-reimbursed drugs as published by the SFK [28]. All drugs were classified by the anatomic therapeutic chemical (ATC) classification [29]. For each drug class, the most frequently used representative was selected (e.g. simvastatin within statins [HMG-CoA reductase inhibitors] and omeprazole within proton pump inhibitors)—48 drugs in total (see Electronic Supplementary Material 1). The side effects of these 48 drugs, as listed in their SPCs at a frequency of at least 1%, from here on addressed as side effects, were collected from Apotheek.nl, a website with online drug information in lay language that can be understood by patients [30]. Thus, the side effects obtained were scored based on the number of drugs multiplied by a weight factor for the frequency as listed in Apotheek.nl (1 for 1–10%, 2 for 10–30%, 3 for ≥30%). Subsequently, the side effects were translated into a total of 165 related symptoms. These symptoms (e.g. nausea, vomiting) were grouped according *to International Classification of Primary Care-Second Edition* (ICPC-2) classification codes by one of the researchers (TS), resulting in 65 symptom categories [31]. Subsequently, the same researcher (TS) ranked the symptom categories in descending order on the scores allocated, and set up a pragmatic cut-off point within the list to comprise the most common symptoms without overloading the patient. Both the symptom categories and cut-off point were independently reviewed by the other researchers (MT, MW, PdS). The symptoms were compared with symptoms listed in the literature, and no further omissions were found. The final set of the 22 most frequently occurring symptom categories was agreed in a consensus meeting of all researchers. Patients could also report additional symptoms if needed.

Finally, all domains were combined into one instrument that was sent to two groups of ten community pharmacists each to check for usability in common practice. This did not result in any changes in the instrument, but yielded meaningful information for its implementation as part of CMRs such as written instructions on how to use patient responses in clinical practice. Additionally, the instrument was pretested in patients eligible for a CMR to assess whether the items were well-understood. Using cognitive interviewing, patients were asked to fill in the form by thinking out loud and supplementary questions to substantiate their answers were asked when needed. In total, six individual interviews were held, with an evaluation after three interviews resulting in slight changes in the instrument. After six interviews no new insights were gained. The cognitive interviews led to textual and layout improvements, rearrangement of the symptoms into a logical order, and simplification of the answer categories in the symptom domain. In this final version of the PROMISE instrument, patients were asked to report all symptoms experienced in the last month (yes, no). They were also asked to indicate whether they associated these symptoms with one of their drugs in use (yes, perhaps, no). Symptoms with the answer 'yes' on the second question are from here on addressed as drug-associated symptoms.

2.2.3 Pharmacist Selection

Pharmacists from 15 community pharmacies participated in this study. They were all users of the same online pharmaceutical care support system, which includes a tool to support the implementation of CMRs. The participating pharmacies were a convenience sample from 11 municipalities, urban as well as rural, spread over The Netherlands. All participating pharmacists were trained and experienced in performing CMRs according to the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) [32], as described in the Dutch guideline for CMRs [14, 15]. Additionally, the pharmacists received written instructions for the sampling of patients and for the data collection for this study.

2.2.4 Patient Sample

Patients were considered eligible for participation following the guideline-based inclusion criteria for CMRs, except that cognitive disability was an exclusion criterion due to the need for a patient to complete the instrument [14, 15]. 'Chronic use of at least five drugs', the main inclusion criterion, was determined by means of the online tool. Subsequently, further sampling was applied by pharmacists based on additional risk factors such as age over 65 years, co-morbidities (e.g. renal dysfunction), decreased adherence and use of risk medication without protective co-medication (e.g. people >70 years using NSAIDs without adequate gastroprotection). Additionally, practical criteria were applied, such as good cooperation with the patient's GP or reimbursement of a fee for the CMR by the patient's health insurance company. A patient's ability to complete the instrument and participate in an interview was determined in cooperation with their GP. The pharmacists invited all selected patients by telephone or mail for a CMR and to take part in the study between September 2014 and September 2015.

2.3 Data Collection

2.3.1 Patient-Reported Symptoms and Drugs in Use

Patients completed the PROMISE instrument at home or in the pharmacy just before the interview. The pharmacists then passed on the completed PROMISE data and information on actual drug use and the patient's sex and age to the researcher, all provided using an anonymous patient code. In The Netherlands, community pharmacists have access to patients' actual drug use through their community pharmacy information system. An actual drug list was retrieved for each patient, from which the dispensed drugs covering the month before completing the PROMISE instrument were considered to be in use.

2.3.2 Side Effects of Drugs in Use

All of the SPC-listed side effects for the drugs in use and their frequencies were retrieved to enable a comparison with the patient-reported symptoms. This was performed in a likewise procedure as in the development of the PROMISE instrument but with some differences. For this purpose, the side effects were primarily retrieved from the Royal Dutch Pharmacists Association's online drug database (KNMP Kennisbank) which contains drug information for pharmacists [33] that is derived from the SPCs [34]. If the KNMP Kennisbank lacked specific information about the frequency of side effects listed for a specific drug, additional information was collected from Apotheek.nl [30]. The information in Apotheek.nl is derived from the data in the KNMP Kennisbank and extended using other sources if necessary to describe patient-oriented information in lay language and to convert clinical manifestations into symptoms. The frequency of side effects is listed by category in the SPCs, e.g. side effects with a frequency of ≥10% are categorised as 'very common', 1–10% as 'common', and 0.1–1% as 'uncommon' side effects [34]. In our study, we only collected information on 'very common' and 'common' listed side effects of all drugs being taken by patients who reported at least one symptom. All side effects, including clinical manifestations, were listed and converted into the corresponding symptom category of the PROMISE instrument independently by two researchers (TS, PdS). Clinical manifestations were translated into one or more of the predominant symptoms in the PROMISE instrument (e.g. hypoglycaemia was converted to change of appetite, trembling, headache, dizziness, tiredness, and sweating). Disagreements between the two researchers were discussed until consensus was reached. If different frequencies were listed for the corresponding side effects in composite symptoms (e.g., 'nausea, vomiting'), the highest frequency was assigned. Thus, obtained 'very common' side effects were compared with the patient-reported symptoms. Patient-reported symptoms that aligned with a side effect of one or more drugs in use are from here on addressed as SPC-associated symptoms.

2.4 Outcome Measures

The following outcomes were measured in this study: the number of patients reporting a predefined symptom, the number of patients reporting this as a drug-associated symptom, and the number of patients reporting a symptom that was a 'very common' side effect in at least one of their drugs in use ('SPC-associated symptom').

2.5 Analysis

All data were registered in an Access® 2007 database (Microsoft Corp., Redmond, WA, USA). Drugs were registered using the 2013 version of the ATC classification system of the World Health Organization [29]. Drugs were mainly registered at the ATC-5 level (of drug substance), except for some drugs such as insulin (A10A) or calcium in combination with colecalciferol (A12AX) that were registered at a higher ATC level. All other composite preparations were registered separately for each of the constituents (e.g. salmeterol and fluticasone).

Numbers of patients reporting a symptom, a drug-associated symptom and an SPC-associated symptom were counted using descriptive statistics. Logistic regression was used to assess the contribution of each additional drug in use that had the symptom listed as a 'very common' side effect (predictor) to the probability of a patient reporting a symptom (outcome), adjusted for sex and age. A p value of ≤ 0.05 was considered statistically significant. Subsequently, a Bonferroni correction for multiple testing was applied with a p value of ≤ 0.0023.

For all SPC-associated symptoms, we counted the numbers of patients using drug classes with these symptoms listed as a side effect and the number of users reporting these symptoms. The outcomes were aggregated at the ATC-4 level, except for drug classes composed of drugs with a different pharmacological profile (e.g. other antidepressants [N06AX]), which were not aggregated but analysed at the ATC-5 level. Drug classes with five or more patients reporting an SPC-associated symptom were considered to be relevant for reporting. In a sensitivity analysis, in addition to 'very common' side effects, 'common' side effects were also included. Percentages of drug users reporting a corresponding SPC-associated symptom were only compared for drug classes with ten or more users with the aim of achieving a meaningful comparison.

Symptoms were counted by means of queries in an Access® 2007 database. Data were exported to SPSS® version 22 (IBM Corp., Armonk, NY, USA) for logistic regression analysis. The data from both queries and statistical analysis were aggregated in tables using Microsoft Excel®, 2007 version (Microsoft Corp.).

3 Results

Of the 228 patients with initial informed consent, 180 (78.9%) provided data to this study. The other 48 subjects either did not answer the PROMISE instrument (32 patients) or withdrew from the study (16 patients). The mean age of these non-responders was 73 years and 52.1% were female. In comparison, the mean age of the 180 included subjects was 73 years (range 43–89 years) and 93 (51.7%) were female. The included subjects used a total of 258 different drugs with a mean of nine per person (range 5–22). The most prevalent drug classes in use were proton pump inhibitors (122 patients), statins (115 patients) and selective β-blocking agents (96 patients) (Table 1).

3.1 Symptoms

Of the 180 included subjects, 168 (93.3%) reported a total of 1102 predefined symptoms in the PROMISE instrument. Sixteen patients (8.8%) reported an additional symptom, e.g. sleeplessness and restless legs. The mean number of predefined patient-reported symptoms was 6.12 with a range from 0 to 19 (Table 2). Patients most frequently reported the following symptoms: 'muscle pain, joint pain' (105 patients), 'weakness, tiredness' (95 patients) and 'dry mouth/thirst, mouth complaints' (79 patients). Patients least frequently reported the following symptoms: 'nausea, vomiting' (17 patients), 'sexual complaints' (21 patients) and 'change of appetite' (23 patients) (Table 3).

3.2 Drug-Associated Symptoms

In total, 304 drug-associated symptoms, with a mean number of 1.69 per patient (range 0–13), were reported by 101 (56.1%) of the 180 patients (Table 2). Patients indicated 27.6% of the 1102 reported symptoms to be drug associated ('yes') and 44.3% to be 'perhaps drug-associated' (71.9% together). The percentage of 'perhaps drug-associated' varied between 33 and 54% for nearly all symptoms, apart from 'bruises, bleedings' for which only 17% of the patients were not sure about a drug association. The following drug-associated symptoms were reported most frequently: 'bruises, bleedings' (46 patients, 65% of 71 patients reporting this symptom), 'dry mouth/thirst, mouth complaints' (34 of 79 patients, 43%) and 'skin complaints, itching' (25 of 68 patients, 37%). The following drug-associated symptoms were reported least frequently: 'muscular weakness' (4 of 40 patients, 10%), 'palpitations' (4 of 36 patients, 11%) and 'change of appetite' (5 of 23 patients, 22%) (Table 3).

3.3 SPC-Associated Symptoms

Of the 180 patients in total, 107 (59.4%) reported 284 symptoms that were mentioned in the SPCs as being 'very common' side effects of in total 65 drugs in use (SPC-associated symptoms). Most frequently reported were 'weakness, tiredness' (57 patients, 58% of the 95 patients reporting this symptoms), 'dry mouth/thirst, mouth

Table 1 Patient characteristics

Characteristics	Patients ($n = 180$)
Number of females (%)	93 (51.7)
Mean age [years (range)]	73 (43–89)
Mean number of drugs in use (range)	9 (5–22)
Number of drugs in use [number of patients (%)]	
5–7	65 (36.1)
8–10	64 (35.6)
>10	51 (28.3)
Most frequently used drug classes (ATC code) [number of patients (%)]	
Proton pump inhibitors (A02BC)	122 (67.8)
HMG-CoA reductase inhibitors (statins) (C10AA)	115 (63.9)
B-Blocking agents, selective (C07AB)	96 (53.3)
Platelet aggregation inhibitors excluding heparin (B01AC)	81 (45.0)
ACE inhibitors, plain (C09AA)	66 (36.7)
Angiotensin II antagonists (C09CA)	60 (33.3)
Thiazides (C03AA)	55 (30.6)
Dihydropyridine derivatives (C08CA)	52 (28.9)
Biguanides (A10BA)	46 (25.6)
Vitamin K antagonists (B01AA)	41 (22.8)

ATC anatomic therapeutic chemical

Table 2 Overview of symptoms reported per patient

Characteristics	Patients ($n = 180$)
Mean number of symptoms reported (range)	6.12 (0–19)
Number of symptoms reported [number of patients (%)]	
0	12 (6.7)
1	16 (8.9)
2–4	42 (23.3)
5–9	73 (40.6)
≥10	37 (20.6)
Mean number of drug-associated symptoms reported (range)	1.69 (0–13)
Number of drug-associated symptoms [number of patients (%)]	
0	79 (43.9)
1	40 (22.2)
2–4	39 (21.7)
≥5	22 (12.2)

complaints' (30 of 79 patients, 38%) and 'eye irritation, vision problems' (24 of 69 patients, 35%) (Table 3). For the drug classes in use by at least ten subjects in the study population, the following SPC-associated symptoms were most frequently reported: aldosterone antagonists—'weakness, tiredness' (reported by 9 of the 12 users; 75%); non-selective monoamine reuptake inhibitors (tricyclic antidepressants)—'dry mouth/thirst, mouth complaints' (reported by 7 of 10 users; 70%); prostaglandin analogues—'eye irritation, vision problems' (reported by 7 of 12 users; 58%); selective β-blocking agents—'weakness, tiredness' (reported by 45 of 78 users; 58%); and high ceiling diuretics—'dry mouth/thirst, mouth complaints' (reported by 12 of 21 users; 57%). In relation to specific drug classes, the SPC-associated symptom 'constipation' was reported by six of nine users of natural opioids (67%) and five of ten users of tricyclic antidepressants (50%) (Table 4).

In the sensitivity analysis for the relation with SPC-associated symptoms, in addition to the 'very common', 'common' side effects were also taken into account. This increased the number of drugs potentially associated with the patient-reported symptoms from 65 to 173. In this analysis, the following SPC-associated symptoms were reported most often for drug classes with at least ten users

Table 3 Patient numbers for reported symptoms, drug-associated symptoms and SPC-associated symptoms

Symptom	Patients	Number of patients reporting a symptom	Number of patients reporting drug-associated symptoms				OR for reporting a symptom per additional drug in use with the symptom listed as a side effect[a,b] [OR (95% CI)]
			Yes	Perhaps	No	Missing	
Change of appetite	All responders	23	5	10	6	2	1.92 (0.80–4.59)
	Users with SPC-associated symptom for ≥1 drug(s)[a]	9	2	4	2	1	
Dry mouth/thirst, mouth complaints	All responders	79	34	33	4	8	1.92 (1.10–3.36)[c]
	Users with SPC-associated symptom for ≥1 drug(s)	30	15	11	1	3	
Nausea, vomiting	All responders	17	6	6	4	1	1.54 (0.96–2.46)
	Users with SPC-associated symptom for ≥1 drug(s)	12	4	5	2	1	
Stomach pain, dyspepsia	All responders	31	10	15	4	2	0 (0–0)
	Users with SPC-associated symptom for ≥1 drug(s)	0	0	0	0	0	
Abdominal pain	All responders	26	10	10	4	2	0.85 (0.34–2.11)
	Users with SPC-associated symptom for ≥1 drug(s)	7	3	3	0	1	
Diarrhoea	All responders	34	9	17	7	1	1.90 (1.14–3.16)[c]
	Users with SPC-associated symptom for ≥1 drug(s)	20	5	12	3	0	
Constipation	All responders	35	14	14	2	5	3.50 (1.67–7.31)[c,d]
	Users with SPC-associated symptom for ≥1 drug(s)	12	7	5	0	0	
Flatulence	All responders	76	18	38	6	14	1.30 (0.18–9.54)
	Users with SPC-associated symptom for ≥1 drug(s)	2	1	1	0	0	
Eye irritation, vision problems	All responders	69	14	33	15	7	1.50 (0.90–2.50)
	Users with SPC-associated symptom for ≥1 drug(s)	24	7	10	6	1	
Palpitations	All responders	36	4	19	10	3	2.60 (0.78–8.65)
	Users with SPC-associated symptom for ≥1 drug(s)	5	2	2	0	1	
Trembling, shivering	All responders	37	6	20	5	6	2.74 (0.83–9.09)
	Users with SPC-associated symptom for ≥1 drug(s)	5	1	2	1	1	
Muscle pain, joint pain	All responders	105	19	41	30	15	0.44 (0.16–1.23)
	Users with SPC-associated symptom for ≥1 drug(s)	7	0	1	4	2	
Muscular weakness	All responders	40	4	20	11	5	0 (0–0)
	Users with SPC-associated symptom for ≥1 drug(s)	0	0	0	0	0	
Headache	All responders	41	5	22	8	6	1.25 (0.88–1.77)
	Users with SPC-associated symptom for ≥1 drug(s)	22	3	10	6	3	
Dizziness, vertigo, fainting	All responders	57	11	29	11	6	1.17 (0.76–1.81)
	Users with SPC-associated symptom for ≥1 drug(s)	23	3	11	4	5	
Weakness, tiredness	All responders	95	18	47	21	9	1.40 (0.90–2.16)
	Users with SPC-associated symptom for ≥1 drug(s)	57	14	25	12	6	

Table 3 continued

Symptom	Patients	Number of patients reporting a symptom	Number of patients reporting drug-associated symptoms				OR for reporting a symptom per additional drug in use with the symptom listed as a side effect[a,b] [OR (95% CI)]
			Yes	Perhaps	No	Missing	
Drowsiness	All responders	59	16	32	7	4	1.30 (0.83–2.04)
	Users with SPC-associated symptom for ≥1 drug(s)	20	7	9	2	2	
Change of mood	All responders	35	7	16	7	5	NA
	Users with SPC-associated symptom for ≥1 drug(s)	1	0	0	1	0	
Sexual complaints	All responders	21	11	7	3	0	1.34 (0.41–4.42)
	Users with SPC-associated symptom for ≥1 drug(s)	4	2	2	0	0	
Bruises, bleedings	All responders	71	46	12	6	7	0.64 (0.12–3.33)
	Users with SPC-associated symptom for ≥1 drug(s)	2	0	2	0	0	
Skin complaints, itching	All responders	68	25	29	10	4	1.52 (0.66–3.48)
	Users with SPC-associated symptom for ≥1 drug(s)	8	3	4	1	0	
Sweating	All responders	47	12	18	10	7	2.70 (1.15–6.33)[c]
	Users with SPC-associated symptom for ≥1 drug(s)	14	7	3	3	1	

NA not applicable, *OR* odds ratio, *SPC* summary of product characteristics

[a] Based on possible associations with all listed 'very common' side effects of drugs in use in all subjects

[b] An OR >1 means that the chance for a patient to report the symptom increases with this factor for every additional drug in use with the symptom listed as a side effect in the SPC

[c] Statistically significant ($p \leq 0.05$)

[d] Statistically significant ($p \leq 0.0023$) after Bonferroni correction for multiple testing

in the study population: anticholinergic inhalants—'dry mouth/thirst, mouth complaints' (symptom reported by 20 of 24 users; 83%); and glucocorticoid inhalants—'muscle pain, joint pain' (reported by 17 of 22 users; 77%). Only 12 of 40 statin users (30%) reported 'muscle pain' as a 'common' side effect (see Electronic Supplementary Material 2).

3.4 Association Between Symptoms and Drugs in Use

Use of a drug with a specific symptom listed as a 'very common' side effect in its SPC statistically significantly increased the probability of a patient reporting this symptom with each additional drug: 'constipation' by 3.50 (95% confidence interval [CI] 1.67–7.31); 'sweating' by 2.70 (95% CI 1.15–6.33); 'dry mouth/thirst, mouth complaints' by 1.92 (95% CI 1.10–3.36); and 'diarrhoea' by 1.90 (95% CI 1.14–3.16). After correction for multiple testing, only the association for added influence of several drugs on reporting 'constipation' remained statistically significant (Table 3).

4 Discussion

Of users of at least five drugs used long-term who were selected for a CMR, 93.3% reported at least one symptom on the PROMISE instrument, which was in line with earlier studies [20, 35]. In total, 1102 symptoms spread over 22 predefined symptom categories were reported by 168 patients. Patient numbers per category varied from 21 patients reporting 'nausea, vomiting' to 105 reporting 'muscle pain, joint pain'. At least one symptom was indicated as being drug associated by 56.1% of the patients, mostly 'bruises, bleedings' (46 patients). In 59.4% of the patients, at least one of their symptoms reported could be traced to a 'very common' side effect of at least one drug in use according to the SPC information. These 'SPC-associated symptoms' were mostly 'weakness, tiredness' (57 patients), with the majority (45 patients) using metoprolol. The patient-reported symptom categories 'dry mouth/thirst, mouth complaints', 'constipation', 'diarrhoea' and 'sweating' were associated with an increasing number of drugs in use that had the symptom listed as a 'very common' side effect in the SPC.

Table 4 Examples of specific drugs/drug classes in patient-reported summary of product characteristics-associated symptoms[a]

Symptom	Drug/drug class[b]	ATC	Number of patients reporting the symptom (% of users of drug from this drug class)	Number of patients using a drug from this drug class with the symptom listed as a side effect[a]
Change of appetite	Blood glucose-lowering drugs, biguanides (metformin)	A10BA	8 (18)	45
Dry mouth/thirst, mouth complaints	High ceiling diuretics (furosemide)	C03CA	12 (57)	21
	Antidepressants, non-selective monoamine reuptake inhibitors	N06AA	7 (70)	10
Nausea, vomiting	Blood glucose-lowering drugs, biguanides (metformin)	A10BA	6 (13)	45
Abdominal pain	Blood glucose-lowering drugs, biguanides (metformin)	A10BA	7 (16)	45
Diarrhoea	Blood glucose lowering drugs, biguanides (metformin)	A10BA	14 (31)	45
Constipation	Natural opium alkaloids (oxycodone)	N02AA	6 (67)	9
	Antidepressants, non-selective monoamine reuptake inhibitors	N06AA	5 (50)	10
Eye irritation, vision problems	High ceiling diuretics (furosemide)	C03CA	11 (52)	21
	Antidepressants, non-selective monoamine reuptake inhibitors	N06AA	5 (50)	10
	Ophthalmologics, prostaglandin analogues	S01EE	7 (58)	12
Muscle pain, joint pain	Bisphosphonates (alendronic acid)	M05BA	6 (57)	9
Headache	Platelet aggregation inhibitors, (dipyridamole)	B01AC	5 (33)	15
	Organic nitrates	C01DA	9 (30)	30
Dizziness, vertigo, fainting	Platelet aggregation inhibitors, (dipyridamole)	B01AC	6 (40)	15
Weakness, tiredness	Aldosterone antagonist (spironolactone)	C03DA	9 (75)	12
	β-Blocking agents, specific (metoprolol)	C07AB	45 (58)	78
Drowsiness	Benzodiazepine derivatives	N05BA	8 (100)	8
Sweating	Antidepressants, non-selective monoamine reuptake inhibitors	N06AA	5 (50)	10
	Other antidepressants, venlafaxine	N06AX	5 (83)	6

ATC anatomic therapeutic chemical

[a] Based on all listed 'very common' side effects of drugs in use

[b] All drug classes (drugs) on the ATC-4 level in the ATC classification system with ≥5 patients reporting a symptom are displayed. The generic drug name is displayed in parentheses when only one drug was involved. Drug classes composed of drugs with a different pharmacological profile (e.g. other antidepressants, N06AX) were not aggregated; when a single drug exceeded the cut-off point the drug name is specified

In this study, we measured all symptoms reported by users of at least five drugs in long-term use via a CMR performed by community pharmacists. Other studies of community pharmacist-initiated CMRs reported only on drug-associated symptoms. Krska et al. [18] named a mean number of 1.9 drug-associated symptoms per patients, which is in line with the mean number of 1.7 per patient found in our study. The study by Krska et al. [18] was performed in a comparative setting of subjects with five or more drugs being used long-term. They identified the symptoms by screening health records in combination with patient interviews rather than with an instrument. Two other studies in the context of a CMR reported considerably lower mean numbers of symptoms of 0.43 and 0.58 per patient [17, 36]. However, they only reported drug-associated symptoms that were confirmed by a pharmacist, which explains the difference from the numbers reported by patients in our study. The lack of overall patient-reported symptoms in these studies hinders reliable comparison.

In evaluating patient-reported symptoms as drug associated, the probability of a drug-related symptom occurring has to be considered [21, 32]. The probability of drug-related symptoms occurring can be derived from the frequencies for the side effects as given in the SPCs. However, the information in the SPC is based on clinical trials in specific patient populations with a short follow-up period, and thus may differ from frequencies in clinical practice [37, 38]. These differences may explain why muscle pain in statin users is more frequently reported in clinical practice than that in the SPCs. In SPCs of statins, 'muscle pain' is listed as a 'common' (1–10%) and for simvastatin even as an 'uncommon' (0.1–1%) side effect, which is in contrast with the 5–20% found in observational studies [39]. In our study, 12 of the 40 users of statins with 'muscle pain' listed as a 'common' side effect reported this symptom. These findings may illustrate the underestimation of side effect frequencies in SPCs. In addition, the time of onset or symptom duration can be used to estimate the likeliness of an association with a drug in use. To illustrate, lower frequencies for diarrhoea were reported with long-term metformin use than at the start of metformin therapy [40, 41].

Inquiring about symptoms regardless of their origin may be advantageous for the pharmacist in effectively improving bothersome symptoms experienced by patients, as patients do not always recognise drug-associated symptoms as such. An earlier study by de Vries et al. [42] noted that 53% of the symptoms reported were associated by patients with at least one of their drugs in use. This is in line with the 71.9% of symptoms that were reported as possibly drug associated ('yes' or 'perhaps') in our study. In 44.3% of the reported symptoms, patients were not certain regarding a drug association. Such uncertainties are more likely when concomitant drugs and diseases are involved [43]. In the patient interview for a CMR, a pharmacist can address such symptoms by assessing drug use, clinical data and co-morbidities using structured tools [14, 21]. Besides drugs, alternative causes for patient-reported symptoms also have to be taken into account, as these symptoms may be due to a prevalent or new disease or be a 'normal' consequence of aging [44, 45]. Such reported symptoms may also indicate an untreated disorder in the patient or a subtherapeutic effect of an existing drug therapy. For instance, although 'weakness, tiredness' is known as a 'very common' side effect of metoprolol and spironolactone, this symptom could also be a sign of worsened heart failure. The likeliness of an alternative cause may differ between symptom categories, as is illustrated by the comparison between the numbers of symptoms and drug-associated symptoms reported in our findings. In our study population, drugs were less often indicated as the causes in unspecific symptoms such as 'weakness, tiredness' than in more specific symptoms such as 'bruises, bleedings'. The latter symptom may well be recognised by patients as a well-known side effect of vitamin K antagonists.

Concomitant use of drugs with the same side effect is believed to contribute to the probability of reporting the corresponding symptom. We found an association between the symptoms 'diarrhoea', 'constipation', 'sweating' and 'dry mouth/thirst, mouth complaints' and each additional drug in use with that symptom listed as a 'very common' side effect in the SPC. Consequently, to alleviate these bothersome symptoms, drug interventions have to be taken into account. Our findings provide insight into the most likely candidates. Users of metformin frequently reported 'diarrhoea', which is a well-known side effect of this drug [40]. In the literature, constipation was shown as a side effect of opioids and tricyclic antidepressants, and this is in agreement with the findings of our study [9, 16, 46]. Tricyclic antidepressants were also found to be a potential cause of 'sweating' and 'dry mouth/thirst, mouth complaints'. In the sensitivity analysis, the latter symptom category was also associated with anticholinergic inhalants, a drug class used by at least five subjects in our study population.

4.1 Strengths

Our study had several strengths. First, patients from community pharmacies all over The Netherlands were included, so the results can be considered to be representative of the population of community-dwelling patients taking at least five drugs in long-term use. Second, the detailed information on actual drug use available at community pharmacies enabled us to evaluate associations between the symptoms reported by patients and the 'very common' side effects of their drugs in use. Third, the use of a cut-off point in the analysis of SPC-related symptoms elucidated the most likely associations between drugs and symptoms reported by patients.

4.2 Limitations

Our approach was not without limitations, the first of which was related to the PROMISE instrument. As PROMISE only contained 22 predefined symptom categories, other symptoms, such as sleeplessness or restless legs, may have been underreported by patients. However, the numbers of predefined patient-reported symptoms are likely to be representative due to the structured development of this list based on the most common side effects of the most frequently used drugs. A second limitation was that the side effects listed in the SPC had to be translated into the symptoms used in the PROMISE instrument. To reduce the risk of interpretation errors, this process was performed

independently by two researchers. Third, as we mainly focused on the most common side effects, we may have missed associations with less common side effects. The inclusion of less common side effects could have shown more potentially SPC-associated symptoms but would have complicated interpretation of our results. Furthermore, as not all potential side effects are listed in the SPCs, a conclusive evaluation would still not be possible. As we focused on patient-reported symptoms, a fourth limitation of our study was that the healthcare professionals' view on potential drug associations was not included. However, this is part of the process of a CMR and should be evaluated in the subsequent trial.

5 Conclusion

Users of at least five drugs in long-term use reported symptoms and indicated drug associations using the PROMISE instrument. For a majority of the symptoms reported, a drug in use with the symptom listed as a 'very common' side effect could be detected in patients' actual use. Especially for 'dry mouth/thirst, mouth complaints', 'constipation', 'diarrhoea' and 'sweating', additional drugs with these side effects in use contributed to patients' symptoms experienced.

Further research is needed to evaluate the use of the PROMISE instrument to verify and ameliorate potentially drug-related symptoms as part of the patient interview in the CMR, and to assess whether this contributes to a reduction of symptoms experienced by patients as a result of their drug therapy.

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Compliance with Ethical Standards

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Conflict of interest Tim W.A. Schoenmakers, Martina Teichert, Michel Wensing, and Peter A.G.M. de Smet declare that they have no conflicts of interest.

Ethical approval All procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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