

The role of the community pharmacist in minor ailments

Focus on uncomplicated urinary tract infection in women

RIAN LELIE-VAN DER ZANDE

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Colophon

The research presented in this thesis was performed at the division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht, the Netherlands.

Cover design: Titia Lelie, www.vrijvanvorm.nl

Photography: Rian Lelie-van der Zande

Layout inside work: Titia Lelie, www.vrijvanvorm.nl

Printed by: Gildeprint, www.gildeprint.nl

Fonts used: Nunito, Ubuntu, Avenir

CIP-gegevens Koninklijke Bibliotheek, Den Haag

Lelie-van der Zande, A.C.A.M

The role of the community pharmacist in minor ailments: focus on uncomplicated urinary tract infection in women

Thesis Utrecht University -with ref. – with summary in Dutch

ISBN/EAN: 978-94-6419-620-7

DOI: <https://doi.org/10.33540/1508>

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The role of the community pharmacist in minor ailments

Focus on uncomplicated urinary tract infection in women

De rol van de openbaar apotheker bij zelfzorg
Focus op blaasontsteking bij vrouwen
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de rector magnificus, prof.dr. H.R.B.M.
Kummeling, ingevolge het besluit van het college voor promoties in het
openbaar te verdedigen op woensdag 23 november 2022 des middags te 2.15
uur door

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You may never know what results
come from your action.
But if you do nothing, there will be no
result.

Mohandas K. Gandhi

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CHAPTER 1

General introduction

Access to medical care has increased considerably in the last century. The downside of this development is that many people consult a physician for symptoms of minor ailments that our ancestors would have resolved with limited resources. The ageing population, a policy of transferring care from hospitals to primary care, and a shortage of general practitioners (GPs) and practice assistants have contributed to excessive demand for primary care. The COVID-19 pandemic further contributed to this overload of general practice.

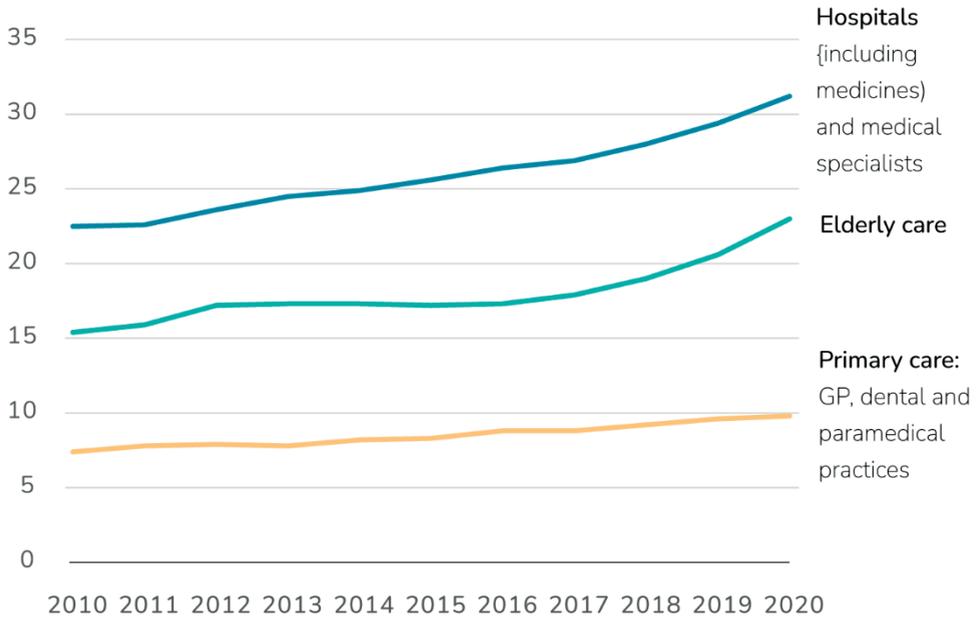
Unnecessary appeal to general practice for minor ailments has decreased the self-reliance of consumers and patients, increasing healthcare costs. Nevertheless, community pharmacists can play an essential role in facilitating effective self-care for minor ailments as they are among the most accessible and well-trusted healthcare professionals by patients [1].

Thus, it is essential to know how patients behave when confronted with minor ailments to increase the self-reliance of consumers and patients, including what they do or do not know about specific conditions and their treatment and prevention. Moreover, it is crucial to know whether healthcare providers, such as community pharmacists and GPs, offer proper self-care support. Finally, more information is required for a shift in primary care of minor ailment consultation and prevention from the GP practice to the community pharmacy.

Foresighted development of healthcare in the Netherlands, 2015 – 2060

Before the COVID-19 pandemic, the National Institute for Public Health and the Environment published a preliminary public health foresight study for healthcare expenditures for 2015–2060 without policy changes [2]. Healthcare expenditures are expected to increase approximately 2.8% per year until 2060, even after population ageing has peaked around 2040. Figure 1 shows that healthcare expenditures for elderly and hospital care increased more than for primary care in the last decade.

Figure 1. Healthcare expenditures 2010–2020 (in billion EUR), excluding expenses for pharmacists and medicines in primary care [3]



One policy is to transfer care from the hospital to primary care to restrict the increasing expenditure in the years to come. Concurrently, the primary care workforce is under pressure. According to the Social and Economic Council, both in the short and long run, the demand for care will correlate with increased healthcare employment opportunities [4]. However, the ratio of employed persons to those unemployed, including the ratio of persons working in healthcare to employed persons, will increase until approximately 2040 [4]. The estimated increase in people working in healthcare is probably unrealistic, which is an important reason to study methods to strengthen the application of self-care. This issue raises the question of whether the transfer of minor ailment care activities of GPs to community pharmacists is possible.

Self-medication means that the consumer alone makes an informed decision whether to purchase a nonprescription medicine, using product information from packaging, the internet and friends or family. When consumers seek help for their decisions, it is termed “facilitated self-medication” (Figure 3). When medicines are purchased in a community pharmacy, pharmacy assistants and pharmacists can facilitate consumer self-care decisions [9].

Nonprescription medicines may either be registered as self-medication products by the Dutch Medicines Evaluation Board (CBG-MEB) [10] or as medical devices after evaluation by a Notified Body according to European regulations [11]. Self-medication products registered by the MEB have a pharmacological effect, whereas self-care medical devices mainly have a physical effect in or on the body. Examples of self-care medical devices are zinc sulphate cream for cold sores and dimeticon lotion for headlice.

Figure 3. Self-care advice by pharmacies



Self-care in the context of medication

Classification of nonprescription medicines

Of all medicines approved for human use by the CBG-MEB, 25% were registered as nonprescription in 2019 [12]. Nonprescription medicines are registered for short-term use, varying from a few days to a maximum of two weeks without GP consultation.

The Dutch MEB registers nonprescription medicines in three classes [10]: (1) pharmacy only (UA = *Uitsluitend Apotheek*), provided under the supervision of a pharmacist with medication monitoring (e.g. for interactions); (2) general sales (AV = *Algemeen Verkrijgbaar*), provided by a drugstore, supermarket and other points of sale and (3) pharmacy and drugstore¹ only (UAD = *Uitsluitend Apotheek en Drogist*), provided by pharmacies and drugstores, available in-person for an additional explanation about medicine use. The balance between the availability and safety of the registration in these three categories, including the role of drugstores and pharmacies, was evaluated with a positive outcome for the registration in classes. However, one of the recommendations was that more attention was needed concerning consumer awareness of the safe use of nonprescription medicines [13].

Reclassification of prescription medicines

The extent of self-care, in part, is defined by the number of active ingredients available as self-care medication. Widening access to medicines through reclassification ('switching') from prescription to nonprescription is an international trend. A qualitative comparison of nine countries showed that enablers included government policy (particularly in the UK), pharmacist-only scheduling (particularly in Australia and New Zealand) and large market size (particularly in the US and Europe) [14]. Local barriers included limited market potential in small countries, one-year market exclusivity and consumer behaviour [14].

¹ Dutch drug stores are consumer-focused shops that stock many self-medication products, health products, products for (personal) hygiene, cosmetics and other consumer goods. In-person or online, druggists can provide consumers with additional explanations about the use of 'pharmacy and drugstore only' self-care medicines.

For example, a study in Germany showed that enabling market factors included the large population and a culture of self-medication. Enabling health system factors included the pharmacy-only category. Some pharmacy factors appeared to enable (e.g. a positive experience after reclassifying emergency contraception), while others appeared to hinder reclassification (e.g. insufficient research on reclassifications). Certain medical factors were enabling (e.g. delayed doctor access and waiting times) while others limited reclassification (e.g. opposition to some reclassifications) [15].

In the UK, a pharmacist can advise pharmacy-only (P) products (e.g. sumatriptan for migraine, mometasone nasal spray for hay fever, hydrocortisone cream for itch and sildenafil for erection disorders) [16].

In Europe, reclassification can be decided on a European or national level [17, 18]. In the case of a European reclassification, the national drug regulatory authority can subsequently decide the nonprescription class of the product. In the Netherlands, most reclassified medicines are classified as pharmacy and druggist only (e.g. levonorgestrel and ulipristal emergency contraception, clotrimazole vaginal cream and tablet, omeprazole, pantoprazole and ipratropium/xylometazoline nasal spray) [19].

Dutch self-care market

In the Netherlands, the self-care market was liberalised in 2009. Thus, in 2020, only 9.1% of nonprescription medicines were purchased at community pharmacies, 75.9% at druggists and 15.0% at supermarkets [20]. In pharmacies, nonprescription medicines are mainly purchased for pain disorders (20.0% of turnover), upper respiratory problems (17.7%), skin and hair problems (15.3%) and gastrointestinal problems (11.7%), next to vitamins and minerals (e.g. vitamin D) [12.1%] [20].

The consumer/patient and self-care

Most nonprescription medicines are purchased by the consumer in a drugstore, supermarket or pharmacy, using product information from packaging, advertisements, friends or family and the internet to decide what to purchase. A recent online survey commissioned by the Dutch self-care industry among 1,132 consumers (52.0% of them 55 years or older) showed that 81.5%

sometimes used nonprescription medicines, and 48.8% of these consumers considered the patient package insert as the most reliable information source, followed by the pharmacy with 22.5%. Of the users of self-care medicines, 59.2% sometimes used it in combination with prescription medication. Of these patients, 82.2% asked for information about the combination or searched for it. In the pharmacy, 46.3% sometimes asked for information, 41.9% always asked and 11.8% never asked. On the internet, 55.7% sometimes searched for information, 21.2% always did and 23.2% never searched for information about nonprescription medicines combined with prescription medicines [21].

This growing empowerment in finding information is also influenced by education and health literacy factors. Having a tremendous amount of information can be confusing; consumers/patients must be able to find reliable information and understand and utilise it. For example, a 2020 study showed that 7.7% of persons from the Dutch Health Consumer Panel had inadequate health literacy and 21.1% had limited health literacy [22]. Persons with low health literacy were less able to deal with health and disease at home. Moreover, these people found it challenging to be an active collocutor during a consultation, needing more care and experiencing worse health outcomes [22]. Notably, men, persons with low education, the elderly (65 years and older), and persons who viewed their health as worse had low health literacy levels [22]. Other Dutch studies found that half of the pharmacy visitors had limited health literacy skills and that more than one-third of the patients admitted to the hospital for surgery had limited health literacy [23, 24].

Most people have high levels of confidence in the self-medication products they take, believing them to be effective and as good as prescription medicines. This belief seems to stem from prior positive use of the product, with most consumers using the same product for subsequent episodes of the same illness [25]. However, they may not be aware of the risks of long-term use.

For instance, a study by the Dutch Health Consumer Panel showed that consumers felt confident about their skills regarding nonprescription medicines but had less confidence in the skills of others. Moreover, consumers who were more confident about their skills preferred nonprescription painkillers to be more generally available. Until consumers themselves realise that they are also 'one of the others', they may overestimate their skills regarding nonprescription medicines[26].

Nevertheless, consumers and patients may have a condition-based question and not know what product to use, or they may have a symptom-based question and not know what minor ailment is causing it. A study indicated that it is vital for consumers to consult with pharmacists to improve consumer awareness of the interactions between nonprescription medicines and chronic medication, including the side effects of nonprescription medicines, to self-medicate appropriately, improving their quality of life [27].

The general practitioner and self-care

When patients have symptoms from a minor ailment and do not know the cause or the appropriate treatment, they may be inclined to consult a GP because they are accustomed to doing that in case of disease symptoms. A GP assistant applies triage and decides whether the patient should be referred to a pharmacist or druggist for a self-medication product on www.thuisarts.nl or to a GP for consultation [28, 29].

Data from NHS England indicated that approximately 20% of the general practice workload consists of patients seeking help for minor illnesses [30]. An online questionnaire study commissioned in 2017 by the Dutch self-care industry showed that approximately 20% of patients prescribed medication had a minor complaint for which self-care medication was available. In contrast, a study based on GP consultations found that 5.6% of all short consultations in 2009 were related to minor ailments [31]. This lower percentage was possibly caused by a strict definition of a minor ailment. Beforehand, four GPs and four pharmacists scored minor ailments from 0% to 100% on whether self-care medication would suffice. Only minor ailments with a self-care score higher than 75% were considered. Of the patients who consulted a GP for a minor ailment in 2009, 56% received a prescription or referral for a self-care medicine [31].

This study was repeated in 2015, and the percentage of consultations was constant, although, over time, an increase in the total number of minor ailment consultations was seen. Of the patients who consulted the GP for minor ailments in 2015, 46% received a prescription for a self-care medicine. According to this study, GPs can suffice with a wait-and-see policy for minor

ailments, provided that patients are instructed when the complaint should be reassessed [32].

Self-care advice by the pharmacy team

Self-care advice on nonprescription medication and the prevention of redundant pharmacotherapy can be considered an essential part of pharmaceutical patient care. Contrary to patient care for prescription medicines, the consumer/patient initiates self-care, makes decisions and is in control. Thus, the consumer/patient must have or receive sufficient information to make responsible choices. The education and training of community pharmacists enable them to translate knowledge about quality attributes of medication and clinical evidence into sound, unbiased advice on self-care products and strategies to the public [1].

Self-care guidelines were developed in the 1990s by the Dutch Association of Pharmacists in cooperation with practising community pharmacists to aid pharmacy teams in providing self-care advice to consumers and patients while preventing these teams from referring patients to a GP unnecessarily. The guidelines were based on WHAM-acronym questions and an additional question about symptoms (in other countries, presented as WWHAM: Who is it for? What are the symptoms? How long have the symptoms been present? Has any action been taken? Has any other medication been taken?). Since 2014, the self-care guidelines have been supported by the Dutch College of General Practitioners.

Community pharmacists are recognised in Dutch law as healthcare providers. They can delegate the provision of (self)-care to pharmacy assistants, who most often are the first point of contact for patients at the pharmacy counter [33]. Pharmacy assistants who have completed a three-year vocational programme advise consumers on the use of nonprescription medicines to treat minor ailments under the responsibility of the community pharmacist. Advising on nonprescription medicines and self-care conditions is part of the competency profile of pharmacy assistants, and they are expected to adhere to guidelines and provide patients and consumers with up-to-date, evidence-based treatment advice to ensure optimal health outcomes [34].

According to national self-care guidelines, pharmacists and pharmacy assistants are trained to ask WHAM questions and question about symptoms to analyse consumers/patients' problems [35]. However, doubts have been raised about using mnemonics in self-care [36-39]. WWHAM is the most common mnemonic and the simplest to remember. Nevertheless, it gives minimal information to establish a differential diagnosis when a symptom-based question is asked. Therefore, it is considered a basic information-gathering tool [7].

Urinary tract infections²

For multiple conditions, community pharmacists can support patients with self-care advice. This thesis focuses on recurring urinary tract infections (UTIs) because of the high prevalence and usage of antibiotics [40-42]. Moreover, in some Canadian provinces, New Zealand and the UK, women with recurring UTIs can consult a trained pharmacist to receive an antibiotic without a physician's prescription [43-46].

In 2016, in the Netherlands, the prevalence of uncomplicated UTI in women was 103.5 per 1,000 patients years, whereas, in 2020, the prevalence was 99.8 [40]. Mostly, uncomplicated UTI is a self-limiting disease that heals within a week. However, an estimated 20%–40% of women who have had one previous uncomplicated UTI episode are likely to experience recurring UTIs [47, 48].

Correct diagnosis is crucial to minimise unnecessary antibiotic prescriptions since the overuse of antibiotics is recognised as the main driver of the emergence and spread of antimicrobial resistance [49]. On the other hand, the undertreatment of an uncomplicated UTI episode may negatively impact the quality of life [50-54]. Moreover, women may be able to recognise an uncomplicated UTI episode, potentially based on experiences of previous episodes of uncomplicated UTI.

² UTI can be uncomplicated or complicated. In the literature, various synonyms for uncomplicated and complicated UTIs are used. Synonyms for uncomplicated UTI are cystitis, acute cystitis, acute uncomplicated cystitis, acute bacterial cystitis, recurring UTI and recurrent UTI. Synonyms for complicated UTI are UTI with signs of tissue invasion, pyelonephritis and pyelitis.

Treatment options should be discussed with the patient, comprising a wait-and-see policy, possibly with painkillers or antibiotic treatment [55]. Another option to be discussed is patient-initiated treatment.

Objectives and outline of this thesis

The overall objective of this thesis is to study self-care advice in the community pharmacy, emphasising epidemiology and necessary preconditions for pharmacists' support of prevention and treatment of recurring UTIs, including patients' knowledge about prevention and treatment and the opinion of GPs and community pharmacists about a shift of treatment and prevention from the GP practise to the community pharmacy.

We studied the current situation of self-care in Dutch community pharmacies (1) by interviewing pharmacists and pharmacy assistants about self-care advice and barriers and facilitators and (2) by a simulated patient study on allergic self-care advice in community pharmacies (Chapter 2).

The current situation of treatment and prevention of (recurring) UTIs in the Netherlands was studied by (1) analysing the prescribing behaviour of GPs based on dispensing UTI antibiotics, (2) investigating the pattern of women returning to the pharmacy for a dispensing of guideline UTI antibiotics over five years and (3) questioning women on their self-management skills for prevention and treatment of recurring UTI (Chapter 3).

Considering that community pharmacists in other countries already have a role in providing UTI antibiotics to women, we studied the possibilities in the Netherlands for such a role by (1) surveying general practitioners' and pharmacists' opinions regarding the patient-initiated treatment of recurring UTIs, (2) surveying pharmacists' opinions regarding a prevention consultation for women with recurring UTIs in the pharmacy and (3) comparing acute cystitis diagnosis in women between two methods, either assessing the acute cystitis symptom score (ACSS) questionnaire or analysing urine test(s) with a dipstick/dipslide in GP practices (Chapter 4).

Chapter 5 discusses the results and provides recommendations for community pharmacists, professional organisations and policymakers.

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CHAPTER 2

Current situation of self-care advice in Dutch community pharmacies

Photo: GP guideline antibiotics for treatment of acute cystitis

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GENEESMIDDEL INFORMATIE CENTRUM

KONINKLIJKE NEDERLANDSE MAATSCHAPPIJ TER BEVORDERING DER PHARMACIE



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CHAPTER 2.1

Barriers and Facilitators for Evidence-Based Self-Care Counselling in Community Pharmacy

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Under review with International Journal of Clinical Pharmacy

Abstract

Background

Community pharmacy is easily accessible for self-care advice, supported by self-care guidelines. Such guidelines were introduced in several countries, including the Netherlands, in the 1990s. Previous studies have shown room for improvement of self-care advice in daily pharmacy practice.

Aim

To map community pharmacists' and pharmacy assistants' views on their role in self-care advice and barriers and facilitators for providing evidence-based advice in the community pharmacy.

Method

Semi-structured interviews were conducted face-to-face or online with pharmacists and assistants using topic guides based on the Theoretical Domains Framework (TDF). Interviews were audio-recorded and transcribed verbatim. Transcripts were deductively analysed to identify barriers and facilitators.

Results

In total, 13 pharmacists and 12 assistants were interviewed to reach data saturation. Overall, important barriers were lacking ready knowledge, lacking collaboration with GPs, time-pressuring due to crowded waiting areas, prioritising the handling of prescribed medications, beliefs that WWHAM questions would always lead to correct advice and consumers' trust in commercial drug information. Important facilitators were availability of guidelines, conversational, process and analytical skills, training and assessment and access to patient records.

Conclusion

Pharmacists should strive for an optimal environment in the pharmacy for self-care advice, such as minimising environmental stressors and providing sufficient time for advice. In addition, they should arrange knowledge and skills training, assessing themselves and their team to improve the quality of self-care advice. Pharmacists should also improve collaboration with GPs and raise awareness of the importance of safe use of self-care products with consumers.

Introduction

According to the World Health Organisation, self-care is the ability of individuals, families and communities to promote health, prevent disease, maintain health and cope with illness and disability, with or without the support of a healthcare provider (1). In self-care for minor ailments, community pharmacists (CPs) can play an important role in supporting individuals with health-informed decision-making, as they are among the most accessible and well-trusted healthcare professionals (2).

In the 1990s, governments worldwide promoted the enhancement of self-care with over-the-counter (OTC) medicines as a way of shifting some healthcare costs onto consumers (3). Nowadays, self-care increasingly is regarded as an option to decrease the burden on healthcare providers since, depending on the definition of minor complaints, 5%–20% of GP consultations are related to minor ailments (4-6).

CPs can provide consumers and patients with evidence-based self-care advice to support their self-care decision-making. In the 1990s, the Dutch professional pharmacists' organisation introduced self-care guidelines, including a protocol containing the WWHAM mnemonic with preventive behavioural actions and medication advice for minor ailments. In total, 23 guidelines were developed (7).

Pharmacy assistants (PAs) who have completed a three-year vocational programme assist the pharmacist by advising consumers on OTC use for minor ailments (8), and CPs and PAs are trained in self-care counselling based on the guidelines during their education. Nevertheless, publications have shown room for improving self-care advice in Dutch pharmacies (9, 10).

CPs' and PAs' perspectives and experiences should be assessed to understand the impact of self-care counselling. Thus, an explorative, qualitative approach was chosen to answer questions about the 'what', 'how' and 'why' of self-care counselling (11). Moreover, theory-based frameworks have been increasingly used to explore healthcare professionals' perspectives on behaviour changes related to practice as they can capture a broad understanding of how a service is integrated into practice (12).

Aim of the study

This study aimed to map CPs' and PAs' views on the role of the community pharmacy in evidence-based self-care advice and barriers and facilitators for providing evidence-based self-care advice.

Ethics approval

This study was approved by the Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University (UPF1901).

Methods

Study design and procedure

This qualitative study used the Theoretical Domains Framework (TDF) during data collection and analysis (13, 14). Semi-structured interviews were conducted with CPs and PAs in community pharmacies.

Topic guide development

Two topic guides were developed for the semi-structured interviews, one for CPs and one for PAs, based on general TDF development studies (14), previous TDF studies in pharmacy (15), and the personal experience of the main author with self-care guideline implementation (16, 17). TDF includes domains that provide a view of the cognitive, affective, social and environmental influences on behaviour (14, 15). This study used the second version of TDF with 14 domains (14).

The topic guides consisted of open-ended questions for each of the 14 theoretical domains with several prompts for in-depth follow-up questions (Supplements 1 and 2). The topic guides started with an introduction to the study and concluded with demographic questions. Questions related to the relationship with GPs, reimbursement and reclassification were discussed exclusively with CPs. After interviewing three CPs and three PAs, the topic guides were refined.

Setting

Dutch law on the medical treatment agreement (WGBO) regards CPs as healthcare providers with an autonomous duty to correctly serve and inform their patients according to current guidelines. CPs can delegate self-care advice to PAs, who normally are consumers' first contact at the counter. In 2021, 30% of 2,000 Dutch pharmacies were owned by a pharmacy chain (18). Four of ten pharmacies employed an additional pharmacist next to the pharmacist-owner or managing pharmacist (19). On average, the equivalent of 8.4 full-time PAs was employed per pharmacy (20).

Study participants

Initially, purposive sampling was applied to identify CPs with a high interest in self-care based on publications in the pharmacists' professional journal. When willing to participate by telephone, each CP was asked to invite one of their PAs. This initial contact was followed by snowball sampling, aiming for diversity in location, type of pharmacy and pharmacists' working experiences. Of the 17 CPs approached, 13 (77%) agreed to cooperate, and appointments were scheduled to interview the CP and the PA. The CPs chose between face-to-face or online interviews. This choice was supported by a study suggesting that completing online interviews is a viable alternative to face-to-face interviews (21). Initially, ten interviews were planned per profession, followed by additional interviews until data saturation was reached (no new information or insights were gained) (22). Data saturation was discussed within the research team after 24 interviews.

Table 1: Characteristics of pharmacies, community pharmacists and pharmacy assistants

Number of pharmacies	13
Type of pharmacy	
chain	2
franchise	4
other (independent pharmacist member of negotiating platform)	7
Location	
town < 50,000 inhabitants	5
town 50,000 – 100,000 inhabitants	4
city > 500,000 inhabitants	4
Number of prescribed medicines dispensed per day	
100-200	2
>200	11
Number of OTC* products sold per day	
<10	1
10-50	8
>50	4
Druggist within a distance of 250 meter of the pharmacy	10
Supermarket selling OTC* products within 250 m of pharmacy	9
Number of participating community pharmacists	13
Female	10
Position	
owner/ pharmacist	3
managing pharmacist	6
locum pharmacist	4
Years of experience in pharmacy	
<5 years	4
5-10 years	4
>10 years	5
Number of participating pharmacy assistants	12
Female	12
Years of experience in pharmacy	
<5 years	4
5-10 years	3
>10 years	5

*OTC = Over-The-Counter = NMP = non prescription medication

Data collection

First, interviews were conducted in July and August 2020. However, interviewing was interrupted by COVID-19 and resumed from November 2021 to January 2022. The face-to-face interviews occurred at community pharmacies. The online interviews were conducted with a secured online meeting tool, Jitsi. All interviews were performed by RL (interview experience) and were audio-recorded with informed consent from the participants. Interviews were transcribed verbatim, coded and entered into NVivo 20 (QSR International, Release 1.5.1).

Data analysis

A coding book was developed, including TDF domains and corresponding items. The transcripts were analysed deductively with NVivo 20, using the TDF domains as coding categories. Within each domain, content analysis was used to identify facilitators and barriers. The deductive phase started with reading the transcripts. The responses were initially attributed to one or more TDF domains, constituting the deductive analysis codes (14). Two researchers (EK and RL) coded three interviews independently using the predefined TDF domain coding book and discussed the results and discrepancies in the first consensus meeting. Disagreements in coding were discussed, an agreement was reached and the coding book was adapted. After this discussion, RL and EK coded the fourth interview independently, and disagreements were again discussed in the second consensus meeting. The coding book was adapted accordingly and discussed with the entire research team. The remaining transcripts were coded by one researcher (RL). The main domains and illustrating quotes appear in the subsequent section.

Results

In total, 13 CPs and 12 PAs from 12 pharmacies were interviewed, and data saturation was reached. Table 1 shows the demographic characteristics of CPs and PAs, along with characteristics of the community pharmacies. The mean interview time for CPs was 41 minutes (33–57 minutes), while for PAs, the mean was 27 minutes (20–36 minutes). Supplement 3 shows a summary of the domain content for TDF sub-themes.

All CPs acknowledged delegating consumer self-care advice to PAs under their supervision. According to all participants, the CP's professional role is to provide self-care advice if needed and to be available for consultations from the PA in complex situations, such as symptoms already present for one to two weeks, young children, indistinct symptoms, underlying conditions, interacting medication use and frequent purchases of painkillers or heartburn medication.

All respondents intended to provide consumers with appropriate advice with or without OTC medication, so they know what to do. Both CPs and PAs intended to provide high-quality advice by using protocols, providing preventive behavioural advice, checking medication safety and advising evidence-based products:

PA03: 'It is my role to advise the patient, help as much as possible and refer the patient to the GP if needed. And, that doesn't mean that they always leave with a product, but that they anyway know what to do'.

When asked about increasing their professional role in self-care as a healthcare provider by widening access to medicines through reclassification ('switching') from prescription to nonprescription, most CPs reported a lack of confidence about diagnosing reclassified medication (*Knowledge, Skills*), and they expected objections from GPs (*Environmental context*). CPs preferred a legal regulation already in use for birth control pills or making agreements with GPs for repeat prescriptions. Most CPs considered training about conditions and differential diagnoses necessary (*Knowledge, Skills*):

CP11: 'We already dispense birth control pills without repeat prescriptions. The GP prescribes the initial prescription, and the patient can get a repeat prescription directly from the pharmacy. It's up to the pharmacy to monitor the use. I don't see any objections to make similar arrangements for medicines such as triptans and intranasal corticosteroids'.

Barriers and facilitators

Table 2 shows barriers and facilitators that CPs and PAs experienced in providing self-care advice.

Some CPs mentioned creating optimal conditions for self-care advice (e.g. knowledge and skills development and facilities in the pharmacy), securing task delegation, providing feedback to assistants and discussing the importance of appropriate self-care advice with team members (*Professional role, Behavioural regulation*):

CP03: 'Ensuring that your team has enough expertise and skills, so you have to impose requirements on the training programme, partly team training, partly personal training. Facilities and product assortment should be state of the art'.

CP01: 'A pharmacist should monitor and correct assistants' advice where needed. When assistants start working in the pharmacy, their knowledge and skills levels are comparable, but after 6 months, the influence of the pharmacist shows; but if pharmacists let it slip, then, yes, of course, quality decreases'.

According to most CPs, during pharmacotherapeutic meetings with GPs, self-care medication was merely discussed when OTC medicines were relevant for treating chronic conditions (e.g. vitamin D or NSAIDs; *Environmental context*). Consumers and GPs perceive pharmacies as more expensive than other OTC outlets (*Environmental context*). GPs with whom the CPs discussed self-care in the pharmacy realised that generic OTC products for which pharmacies

CP06: 'I never discussed self-care with the GPs, and they may very well not know what we do. But, I hope they have any idea of our pharmacy providing self-care advice'.

mostly advise are less expensive than brand products. One pharmacist agreed with GPs on a local formulary based on national self-care guidelines and agreed on measuring the decrease in GP consultations. However, most pharmacists doubted whether GPs were aware of pharmacy self-care advice (*Environmental context*):

Both CPs and PAs emphasised the importance of the availability of and adherence to national self-care guidelines for correct evidence-based self-care advice (*Knowledge*). A barrier was that most assistants were unaware of guideline medication updates because of a lack of attention in the pharmacy. Some CPs assigned a team member to track guideline updates and new product introductions or preferred central updates in an electronic decision-support system. Most participants thought their ready knowledge was reasonable, but some CPs mentioned a barrier: PAs' and CPs' ready knowledge was insufficient to provide the correct advice for all self-care requests (*Knowledge*):

CP01: 'We should pay more attention to ready guideline knowledge at the counter'.

In contrast, most PAs did not mind the lack of thorough guideline knowledge because, according to them, they knew where to find information when needed (*Knowledge*). PAs reported that they asked their colleagues or the CP for advice when their knowledge at the counter was insufficient (*Social influences*). At the counter, only a few PAs searched for information online, while others thought this approach was unprofessional.

All participants responded that they applied the WWHAM protocol for problem analysis. Nevertheless, CPs thought that the extent of the advice could depend on the PA at the counter. To achieve more straightforward advice, some pharmacies used an electronic decision-support system for asking WWHAM questions since the system also considers preventive behavioural actions and provides first- and second-choice medications according to the guideline. Most CPs and all PAs thought that the correct advice would be provided when WWHAM questions were asked for condition-based, symptom-based and product-based requests. However, CPs who participated in a simulated patient programme mentioned a barrier: WWHAM questions were not always sufficient for symptom based requests (*Knowledge*):

CP10: 'No, I don't think that WWHAM is always sufficient. We learned that from a simulated patient visit on a symptom-based request in our pharmacy. We did not grasp the catch'.

Table 2: TDF domains with barriers and facilitators for providing self-care advice

TDF domain: Knowledge	
Barriers	Facilitators
<ul style="list-style-type: none"> • Lack of ready knowledge of minor ailments • Believing that WWHAM questions always lead to correct advice according to the guideline • Lack of guideline update communication 	<ul style="list-style-type: none"> • Availability of self-care guidelines • Accessibility to computerised protocols for minor ailments and pharmacy-only products • Assigning CPs¹ or PAs² responsible for updates and product introductions • Regular guideline advice updates • Team app for communicating updates and new product introductions or weekly/monthly newsletter • Availability of training on self-care guidelines during CP¹ and PA² education • Regular on-the-job training from CPs¹ (i.e. in work meetings) • Availability of web-based training programs • Annual training on seasonal complaints
TDF domain: Skills	
Barrier	Facilitator
<ul style="list-style-type: none"> • Lack of skills training • Lack of skills to retrieve sufficient information from consumers/patients • Information about different cultural backgrounds and attitudes towards pharmacists lacking in PA² and CP¹ education 	<ul style="list-style-type: none"> • Optimal conditions for self-care advising, such as personal development plans and team training • Presence of conversation (verbal and nonverbal), process and analytical skills • Roleplaying within the team or with trainees • Assessing patient self-care skills by web-based testing and simulated patient visits
TDF domain: Professional role and identity	
Barrier	Facilitator
<ul style="list-style-type: none"> • CPs¹ underestimating the importance and difficulty of provision of self-care advice 	<ul style="list-style-type: none"> • Actively offering advice on self-care and lifestyle • CPs¹ creating optimal pharmacy conditions for self-care advice by PAs² and securing task delegation
TDF domain: Beliefs about capabilities	
Barrier	Facilitator
<ul style="list-style-type: none"> • Lack of active CP¹ support for knowledge and skills training 	<ul style="list-style-type: none"> • PAs' intrinsic motivation • PAs feeling capable due to available information and support from colleagues and CPs¹ • Awareness of follow-up questions in addition to WWHAM for correct problem analysis and self-care advice • Attention to empathic staff attitudes • Realising the limits of one's knowledge

TDF domain: Optimism**Barrier**

- Lack of recognition of the added value of self-care advice in pharmacy from policymakers and healthcare insurers

Facilitator

- Consumers/patients return to the pharmacy for self-care advice based on earlier advice
 - Increase of recognition of self-care advice and the added value of pharmacy by CPs¹ communicating about minor ailments and self-care online or in journals
-

TDF domain: Beliefs about consequences**Barrier**

- Compromised medication safety by lack of self-care products
- Registration in electronic patient records
- Less trust from patients and consumers in information based on guidelines than in commercial drug information (e.g. from the internet, advertisements, commercials)
- Less critical alternatives available (asking fewer questions) for consumers to purchase self-care products

Facilitator

- Adding self-care products to electronic patient records enabling clinical risk management (e.g. interactions, contraindications)
 - Appropriate self-care advice may prevent minor ailments from developing into diseases
 - Preventive behavioural advice may help to prevent or decrease minor ailment symptoms after stopping self-care medication
 - Appreciating the initiative of the consumer/patient to research products (e.g. on the internet), thereby improving the attitude of consumers/patients towards advice for an evidence based alternative
-

TDF domain: Reinforcement**Barrier**

- Self-care product registration in electronic patient records requiring non-reimbursable time
- Additional workload for self-care advice not covered by margin from generic self-care products
- Lack of public communication campaign about the added value of self-care advice in pharmacy

Facilitator

- CPs¹ and GPs³ working together to measure the added value of self-care advice in the pharmacy by showing decrease of GP³ consultations and healthcare costs
-

TDF domain: Intentions**Barrier**

- Time pressuring by prioritising dispensing of prescription medicines or crowded waiting area, leading to assistants paying less attention to problem analysis questioning and registering self-care medicines in the pharmacy information system

Facilitator

- Adjusting problem analysis questioning to the consumers depending upon openness to self-care advice
- Adding self-care products to electronic patient records; at least NSAIDs for patients with cardiovascular disease, elderly patients and home-care patients
- Providing preventive behavioural advice according to self-care guidelines

- Registration of pharmacy-only questionnaires in the pharmacy information system

TDF domain: Goals
Facilitator

- Providing easy and timely access to self-care advice in pharmacy
- Striving for high-quality pharmaceutical care
- Clinical risk management for patients using chronic medications or having potential contraindications to secure medication safety

TDF domain: Memory, attention and decision processes
Barrier

- Asking WWHAM questions without incorporating spontaneous information from consumer/patient
- Lack of support for correct appraisal of answers to questions

Facilitator

- Structured advice according to protocols in self-care guidelines
- Practising self-care cases in the pharmacy with trainees or team practice during work meetings to iterate knowledge and skills
- Stickers on pharmacy-only self-care products and products that interact with chronic medications

TDF domain: Environmental context and resources
Barrier

- Priority for dispensing of prescription medicines prohibiting asking out problem analysis questions
- Priority for dispensing of prescription medicines prohibiting self-care product registration in electronic patient records
- Consumers/patients not open to receiving advice
- Language problems
- Patient' attitude towards self-care advice, depending on cultural background
- Consumers/patients with low health literacy level
- Lack of privacy at the counter
- Image with GPs³ and consumers/patients that products in the pharmacy are more expensive than at the druggist
- Effort and time needed to build good relationship with GPs³
- Lack of pharmacotherapeutic meetings with GPs³ about minor complaints as the main subject

Facilitator

- Availability of sufficiently private consultation areas (consulting room or privacy counter)
 - Sufficient distance and separation between counters to provide more privacy
 - Background music in the waiting area
 - Measuring loudness of PAs' voices at the counter and listening to consultations at the counter in the waiting area
 - Communicating indirectly about privacy-sensitive issues when privacy is limited
 - Pharmacy team familiar with various languages in areas with patients from different cultural backgrounds
 - Google Translate app or translator by telephone for communicating when language is not spoken in the pharmacy
 - Visual and verbal communication with low-literacy patients
 - Availability of an electronic pharmacy information system to check interactions and contraindications on the patient level
 - Organising logistic processes in the pharmacy and implementing innovative
-

- Lack of healthcare provider profiles of CPs¹ for consumers/patients
- logistic developments to provide time for self-care advice
- Agreement with GPs³ in pharmacotherapeutic meetings on self-care protocols in the pharmacy and reciprocal referral policy
- Agreement with GPs³ on registering self-care medicines in patient medication records: specific products and patients
- Product prices discussed with GPs³ in pharmacotherapeutic meetings, comparing generic and brand products
- Offering consumers/patients a choice of more and less expensive products with information about effects and prices

TDF domain: Social influences

Facilitator

- Team members supporting one another in providing self-care advice
- CP¹ available for advice on complex situations
- Spontaneous positive feedback from patients
- Positive feedback from GPs³ after referral

TDF domain: Emotion

Barrier

- Disappointment when consumers are not open to preventive behavioural advice

Facilitator

- Satisfied customer who follows up on advice providing positive feeling

TDF domain: Behavioural regulation

Barrier

- PAs² not accepting responsibility when receiving feedback

Facilitator

- Discussing project results (e.g. pharmacy only product registration) or knowledge/skill test results including assessment of opportunities for improvement
- CP¹ providing feedback to PA immediately after incorrect self-care advice
- CPs¹ encouraging PAs² to share new information with colleagues
- PA² encouraging trainees and starting PAs to listen to self-care advice provided by experienced PAs

CP¹ = community pharmacist; PA² = pharmacy assistant; GP³ = general practitioner

Next to the knowledge of the guidelines, PAs and CPs mentioned the following important skills for appropriate advice: (1) verbal and nonverbal conversational skills, such as maintaining eye contact, retrieving sufficient information from consumers, asking open-ended questions and shared decision-making; (2) process skills, such as explaining when using a tool or consulting a colleague, deviating from the strict WWHAM order by integrating spontaneous consumer information and advising consumers to return when having questions; and (3) analytical skills, such as the ability to interpret answers and estimating when and how long to ask follow-up questions (*Skills*):

CP04: 'Knowledge, of course, relating to the content but also to products, and communication skills of course, that you are able to ask open-ended questions and follow up on them and the ability to convey it well'.

PA03: 'You have to listen carefully and listen between the lines because they provide a lot of information spontaneously'.

PA03: 'You always keep eye contact, and you explain to the consumer what you are doing'.

CP10: 'We trained to customise our advice when implementing the Consultation guideline, trying to attune to what people need, and we found it quite hard'.

PAs thought that providing correct advice from colleagues was not defined by years of experience in the pharmacy but depended on intrinsic motivation to maintain and improve knowledge and skills while working (*Beliefs about capabilities, Knowledge, Skills*). CPs and PAs mentioned learning about minor ailments from the guidelines during their pre-graduate training, although all reported they learned most in pharmacy practice by listening to experienced PAs (*Social influences*). PAs also mentioned that during education, the emphasis was on communication skills instead of ready knowledge (*Skills*). CPs who implemented knowledge and skills development and assessment facilitated it mainly by organising web-based training and testing, patient-simulated visits, on-the-job training, discussing assessment results in work meetings, assigning accountable PAs and CPs and communicating guideline updates and product introductions.

Some CPs and PAs reported roleplaying within the pharmacy team and interns (Skills):

PA10: 'We also practice when we discuss a minor ailment during work meetings .We always see to it that we discuss that and update our advice accordingly'.

PAs noticed that consumers were unaware of the healthcare provider role of CPs and sometimes had less confidence in evidence-based information from the pharmacy than from advertisements, commercials and the internet (*Beliefs about consequences*). Some CPs genuinely believed that the pharmacy team could help patients distinguish between reliable and unreliable information. However, PAs thought it important to appreciate consumer efforts to search out information before discussing an evidence-based alternative. Access to electronic patient records and the ability to monitor interactions with chronic medications and contraindications was a facilitator for medication safety and an important added value to the pharmacy (*Beliefs about consequences*). Moreover, PAs reported checking the legally required appropriateness of pharmacy-only medications with a questionnaire (*Memory, attention and decision processes*):

PA05: 'We have a sticker or label on OTC products. A yellow sticker tells us the product has to be checked for interaction with chronic medication, and we also have blue stickers for pharmacy-only products; we check these products with a questionnaire'

PAs noticed that consumers who did not appreciate being asked questions switched to other OTC outlets where fewer questions would be asked. Most PAs mentioned they did their best, but it was the consumers' responsibility if they did not appreciate the advice (*Beliefs about consequences*):

They don't have time nor feel like answering our questions; they think that pharmacy is always asking questions; they prefer to get it at the druggist or supermarket'.

Participants thought that good advice with or without self-medication in the pharmacy might prevent the development of chronic disease and thereby save costs for society (*Beliefs about consequences*). CPs thought that self-care advice and checking medication safety was a barrier, requiring time that is not reimbursed or covered by margin for generic self-care medication (*Reinforcement*). CPs also experienced a barrier in the lack of recognition for the added value of self-care in the pharmacy by GPs, consumers, patients and healthcare insurers (*Optimism*).

Environmental barriers, such as time pressure caused by a crowded waiting area and prioritising dispensing of prescribed medicines are reasons for omitting WWHAM questions. According to a CP, implementing innovative logistic interventions such as central filling and paperless workflow solutions might facilitate providing time for self-care advice and on-the-job training (*Environmental context, Skills*). A lack of privacy at the counter was a barrier for PAs to retrieve sufficient information (*Environmental context*). Participants observed different perceptions of consumers about privacy in the waiting area. In some pharmacies, consumers appreciated the offer of a consulting room, whereas, in other pharmacies, consumers felt embarrassed visiting it. Some pharmacies introduced background music in the waiting area, but this may affect PAs concentration when advising. Moreover, PAs experiencing the loudness of their voice by sound measurement and listening to consultations at the counter in the waiting area were mentioned as facilitators.

Respondents mentioned language problems and some consumers from different cultural backgrounds having more confidence in a GP from their country of origin as a barrier (*Environmental context, Skills*). Team members speaking various second languages, using Google Translate and interpreting by telephone were actions to overcome language problems.

Discussion

Overall, important barriers to evidence-based self-care counselling were CPs' and PAs' lack of ready knowledge and collaboration with GPs. Further barriers included beliefs that WWHAM questions would always lead to correct advice, time-pressuring by the priority assigned to prescribed medications or by crowded waiting areas and consumers having more confidence in commercial drug information than in evidence-based advice from the pharmacy. Important facilitators were availability of guidelines, conversation, process and analytical skills, training and assessment and access to patient records.

Knowledge can be improved by training and assessment and should include diagnosing minor ailments and preventive behavioural advice. This finding aligns with an earlier study that recommended a structured training approach for the entire community pharmacy team to promote outcomes and deliver robust, high-quality minor ailments services (23). Our study found that CPs over-relied on the WWHAM mnemonic for problem analysis. Mnemonics might allow for standardising the information gained from the patient, but interpreting the acquired data might be problematic (24). Problem analysis needs follow-up questions, correct problem identification and adequate problem-solving (25, 26). Our findings align with earlier research findings that CPs show poor clinical reasoning due to an overreliance on protocol-driven questioning (27, 28).

According to participants, registering self-care products in electronic patient medication records enables clinical risk management (e.g. by generating alerts for patients with concomitant morbidity or reduced renal function). As identified in an earlier study, CPs tend to put medication safety first (29). Their main motivation is the health and well-being of their patients, not financial incentives (30). Earlier research has demonstrated that safety and effectiveness are important factors for consumers when purchasing OTC products (31). Therefore, CPs should raise public awareness among consumers and patients about how pharmacies can facilitate the safe and effective use of OTC products (32). Informing consumers about the background of safety related questions in the pharmacy and the reasons to record OTC products in the patient file could improve the perception of the added value of self-care advice in the pharmacy.

Widening access to medicines through reclassification ('switching') from prescription to nonprescription is an international trend (33-35). In the Netherlands, OTC medicines consist of three classes: (1) pharmacy only, (2) pharmacy and druggist only, and (3) general sales provided by druggists, supermarkets and other OTC outlets. This study showed that most CPs were not in favour of reclassifying prescription medicines but preferred being able to rely on a primary GP diagnosis and subsequently repeat the GP prescription.

Participants observed different attitudes of consumers about privacy in the waiting area and visiting a consultation room. In self-care, a lack of felt privacy might be a barrier to retrieving sufficient information from consumers, depending on the symptoms, minor ailments and consumer privacy values (36). Sufficiently private areas at the counter for private pharmacy discussions, could be a solution to address varying views on privacy in the pharmacy (36). Moreover, preventing sound reflection by sound absorbing materials may improve privacy conditions in pharmacy.

Strengths and weaknesses

A major strength of the study was that we included the perspective of both CPs and PAs. Furthermore, we found enough CPs and PAs from various backgrounds (e.g. pharmacy types, location, pharmacist positions and years of experience) willing to cooperate during this strenuous period. The number of interviews was sufficient to reach data saturation (11). In general, the perceptions on barriers and facilitators from CPs and PAs aligned well which added to the data saturation.

The most important weakness of the study was that the topic guides were not piloted with CPs and PAs. Since the first six interviews only led to changes in the order of starting questions, we included all interviews in the analysis.

Conclusion

CPs should strive for an optimal environment in pharmacy to improve the quality of self-care advice by arranging training and assessing knowledge and skills for themselves and their team, providing sufficient time for advice by minimising environmental stressors. CPs should improve collaboration with GPs and raise awareness of the importance of appropriate use of self-care products with consumers.

Acknowledgements

The authors thank the community pharmacists and pharmacy assistants who were willing to share their views on provision of self-care advice.

Funding

No funds, grants, or other support was received.

Conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author's contribution

RL wrote the concept/protocol of the study, (performed the interviews,) analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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Supplementary material

Supplement 1: Topic List Community Pharmacists

Questions	Prompts
What do you understand by the term 'self-care'?	
What do you consider to be the professional role of the pharmacist in self-care?	<ul style="list-style-type: none"> • Attitude of GPs towards self-care advice from pharmacy • Attitude of pharmacist towards self-care advice from druggists. • Difference between self-care advice from pharmacy and from druggist • Professional role of pharmacy assistant
What do you consider to be the importance of self-care advice compared to pharmaceutical care with regard to prescription medicines (e.g. dispensing process, medication review)?	<ul style="list-style-type: none"> • Who delivers self-care advice • Priority
How is the self-care process organised in pharmacy?	<ul style="list-style-type: none"> • Task allocation
What kind of self-care requests do consumers and patients make at your pharmacy (e.g. product-, condition- or symptom-based)?	<ul style="list-style-type: none"> • Team agreement on how to handle these questions • Types of consumers visiting pharmacy for self-care advice
What barriers do you meet when advising on self-care?	<ul style="list-style-type: none"> • Hurried customers • Privacy sensitive minor ailment • Other customers listening in • Intense work pressure • Staff shortages • Training • Financial barriers • Remuneration • Dealing with barriers • Factors that encourage attention to self-care • Use and review of supporting materials
Self-care guidelines include preventive behavioural advice. What is your opinion on that?	<ul style="list-style-type: none"> • Dealing with preventive behavioural advice for minor ailments
What skills does one need to provide an appropriate self-care advice?	<ul style="list-style-type: none"> • Conversation skills • Decision-making • Asking follow-up questions • Ready knowledge, also of the team • Basis of ready knowledge • Training during education • Updating of knowledge • Training of self-care knowledge and skills

	<ul style="list-style-type: none">• Assessment of self-care knowledge and skills
What are benefits of an appropriate self-care advice for you, the pharmacy team, the GP and the customers?	<ul style="list-style-type: none">• Cost/benefit ratio
How do you feel after providing a customer with a self-care advice?	<ul style="list-style-type: none">• Explanation
The UK has a Pharmacist-Only category for medicines such as triptans, sildenafil, corticosteroid inhaler. Do you see opportunities for such a category in the Netherlands?	<ul style="list-style-type: none">• Requirements for implementation
Is there any self-care topic that we missed and that you would like to discuss?	

Supplement 2: Topic List Pharmacy Assistants

Questions	Prompts
What do you understand by the term 'self-care'?	
What do you consider to be the professional role of the pharmacy assistant in self-care?	<ul style="list-style-type: none"> • Role of the pharmacist according to the assistant • Attitude of assistant towards self-care advice from druggists. • Difference between self-care advice from pharmacy and from druggist • Referral to GP
What do you consider to be the importance of self-care advice compared to pharmaceutical care with regard to prescription medicines (e.g. dispensing process, medication review)?	<ul style="list-style-type: none"> • Who delivers self-care advice at the counter • Priority of self-care advice
How is the self-care process organised in pharmacy?	<ul style="list-style-type: none"> • Task allocation
What kind of self-care requests do consumers and patients make in your pharmacy (e.g. product-, condition- or symptom-based)?	<ul style="list-style-type: none"> • Team agreement on how to handle these questions • Types of consumers visiting pharmacy for self-care advice • Self-confidence
What barriers do you experience when advising on self-care?	<ul style="list-style-type: none"> • Hurried customers • Privacy sensitive minor ailment • Other customers listening in • Intense work pressure • Staff shortages • Training • Dealing with barriers • Factors that encourage attention to self-care • Use and review of supporting materials
Self-care guidelines include preventive behavioural advice. What is your opinion on that?	<ul style="list-style-type: none"> • Dealing with preventive behavioural advice for minor ailments • Team agreements
What skills do you need to provide an appropriate self-care advice?	<ul style="list-style-type: none"> • Conversation skills • Decision making • Asking follow-up questions • Ready knowledge, plus ready knowledge of colleagues • Basis of ready knowledge • Training during education • Updating of knowledge • Training of self-care knowledge and skills

	<ul style="list-style-type: none">• Assessment of self-care knowledge and skills
What do you do when experiencing problems providing self-care advice?	<ul style="list-style-type: none">• Consultation of colleague, when?• Consultation of the pharmacist, when?• Agreements within the team about when to consult the pharmacist
How do you feel after providing a customer with a self-care advice?	<ul style="list-style-type: none">• Explanation
Are there any self-care topics that we missed and that you would like to discuss?	

Supplement 3: Summary of domain content for TDF sub-themes

TDF domain: Knowledge

An awareness of the existence of something

Sub-theme: Knowledge

- CPs: Knowledge based on national guidelines and implemented in PA and CP education although more attention is paid to communication skills and knowing where to find information than on ready knowledge.
CPs and PAs thinking their ready knowledge is reasonable; self-care curriculum during education.
- PAs: mention knowledge gaps, e.g. seasonal complaints, high number of interactions of OTC medicines and chronic medication, updates of guidelines and new product introductions.
- CPs: WWHAM questions not always sufficient, important to ask supplementary questions. Guideline summaries and PO questionnaires electronically available, limited awareness of updates.

Sub-theme: Procedural knowledge

- PAs: use of WWHAM; electronic protocols support shared decision making; if available, generic product advised with explanation that brand products are more expensive.
-

TDF domain: Skills

An ability or proficiency acquired through practice

Sub-theme: Skills

- CPs and PAs: verbal and nonverbal communication skills, process skills such as eye contact when using an electronic device, ability to interpret answers and estimate when and how long to continue asking questions and ability to communicate with patients from different cultural background or speaking foreign languages e.g. in holiday regions were mentioned.

Sub-theme: Skills development

- CPs: limited number of pharmacists had a policy on training, online or in pharmacy. Lack of self-care curriculum in CP specialist education.
- CPs and PAs: Some pharmacies practise roleplay, mainly with trainees.
- PAs: Trainees learn most in pharmacy if guidance is available, education more theoretic; important to give trainees opportunity to gain experience at the counter under supervision.

Sub-theme: Skills assessment

- CPs and PAs: Online programs for assessment and simulated patient visits program available, all not in regular use. When in use also team discussion of results.
-

TDF domain: Social/ Professional role and identity

A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting

Sub-theme: Group identity

- CPs: self-care medication incidentally discussed in pharmacotherapeutic meetings with GPs when relevant for patients with chronic medication, doubts about knowledge of GPs of self-care advice in pharmacy
- PAs: good image of pharmacy by providing good advice, and doing this at all times.

Sub-theme: Professional boundaries

- CPs and PAs: important to know when to refer to GP, based on guidelines.

Sub-theme: Professional identity

- CPs: in pharmacy better expertise and medication safety for patients with chronic medication, and contra-indications (e.g. children, pregnancy, breastfeeding).

Sub-theme: Professional role pharmacy assistant

- CPs: PAs are an extension of the pharmacist, have more direct contact with consumers/patients and provide self-care advice.
- PAs: taking care that patients leave the pharmacy contented with a good advice and knowing what to do, referred to GP if needed; adding OTC products to patient record for patients with chronic medication, at least patients with cardiovascular diseases; check of PO medication using a questionnaire.

Sub-theme: Professional role pharmacist

- CPs: pharmacists provide self-care advice and should delegate and secure, monitor, and adjust self-care advice, discussing the importance of self-care for pharmacy and creating optimal conditions for knowledge and skills development and facilities in pharmacy.
- PAs: CP should be available for consultation on complex issues and provision of guideline updates.

TDF domain: Beliefs about capabilities

Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use

Sub-theme: Professional confidence

- CPs: quality of advice depending on which PA advises but confident that correct advice is given when WWHAM is asked according to protocol.

Sub-theme: Self-confidence

- CPs: confident they can provide self-care advice, mainly because they think their ready knowledge is reasonable but if necessary they know where to find information.
- CPs: opinion about reclassification of medication from prescription to PO, e.g. of triptans, intranasal corticosteroid for hay fever or hydrocortisone cream: lack of confidence in diagnosing skills; preferring to be enabled to repeat GP prescription and willing to monitor medication use. GP should mention the diagnosis on the prescription, the pharmacist would have to review these requests himself. Moreover, pharmacists would need training about conditions and differential diagnoses.

Sub-theme: Perceived confidence

- PAs: confident their ready knowledge is reasonable, think they can provide better advice than the druggist, based on personal experience when visiting the druggist. They also know where to find information if necessary.
- CPs: some PAs having natural talent for advising, young PAs
- often having to seek information, older PAs having more expertise.
- PAs: confidence of colleagues not defined by years of experience but depending upon intrinsic motivation for knowledge development and eagerness to learn.

TDF domain: Optimism

The confidence that things will happen for the best or that desired goals will be attained

Sub-theme: Optimism

- CPs: self-care in pharmacy deserves a prominent place in society; measuring and showing added value of self-care advice in collaboration with GPs may increase recognition in GPs, consumers, patients and healthcare insurers; belief of users of electronic protocols that this supports PA independent advice.
- PAs: belief that consumers are provided with correct advice, that asking WWHAM questions will lead to correct advice and that consumers will revisit for other complaints.

TDF domain: Beliefs about consequences

Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation

Sub-theme: Outcome expectancies

- CPs: increase of patient safety by adding self-care medication to patient file; patients can buy self-care medication at other OTC outlets if it's not clear to them why PA asks questions; ample information available on the internet but guidance from pharmacy needed to distinguish between reliable and unreliable information; a minimal advice, e.g. maximum dosage paracetamol or instructions for use, should always be provided; good advice with or without self-medication in pharmacy may prevent development into a chronic disease and high costs for society; self-care advice may decrease GP consultations.
- PAs: if you keep calm and smile when patients complain, all will turn out fine; important that consumers themselves try to decrease their complaints but sometimes it is better not to wait too long to consult the GP to prevent it from turning into a more serious disease; if patients insist on buying a product that may be not an optimal choice, they can also buy it at the druggist, preventive behavioral actions may prevent symptoms re-emerging after stopping self-care medication, consumers may trust evidence based advice from pharmacy less than commercial drug information (e.g. internet, commercials, advertisements), consumers are happy when you take time to advise them; appreciate the initiative of the consumer/patient to research products (e.g. on the internet) to improve the attitude of consumers/patients towards advice for an evidence based alternative

TDF domain: Reinforcement

Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus

Sub-theme: Perceived confidence

- CPs: good self-care advice leads to a better profile, to customer satisfaction and returning customers, may lead to less GP consultations, can make the profession of PAs more attractive, helps the patient to recover.

Sub-theme: Reinforcement

- CPs: self-care advising and checking medication safety take time which is not reimbursed nor covered by margin on generic self-care medication; pharmacists tend to lack commercial interest, most revenues from prescription medicines; GP should be compensated if self-care by GP is transferred to pharmacy (relatively easy GP consult with reimbursement comparable to normal consult).
- PAs: consumers should know they can consult the pharmacy for minor ailments and the added value of the pharmacy, specifically patients using chronic medication.

TDF domain: Intentions

A conscious decision to perform a behaviour or a resolve to act in a certain way

Sub-theme: Intentions

- CPs and PAs: providing high quality advice by using protocols, and providing preventive behavioural advice and evidence based products; medication safety improved by adding self-care to patient file, at least NSAIDs (PO – medication) and for elderly and home-care patients; asking about user of product request and advising at least on usage and max dosage; making time for advice even if that leads to working overtime; in case of high workload only most important questions.

TDF domain: Goals

Mental representations of outcomes or end states that an individual wants to achieve

Sub-theme: Goal target setting

- CPs and PAs: always checking interactions and contra-indications for elderly patients and adding OTC products and PO self-care medication to patient file; provision of high quality advice; contribution to safe and effective use of self-care products.

TDF domain: Memory, attention and decision processes

The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives

Sub-theme: Decision making

- CPs: agreement with GPs on guidelines based formulary supports reciprocal referral.
- CPs and PAs: self-care and PO-protocols available for questioning, advice with or without medication and referral to GP, electronic protocols supporting PA in decision making and providing of uniform advice.

Sub-theme: Memory attention

- CPs and PAs: stickers available on self-care products with potential interactions support use of PO questionnaire and interaction checks in pharmacy information system; practising and discussing self-care cases in pharmacy to repeat knowledge and skills.

TDF domain: Environmental context and resources

Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour

Sub-theme: Environmental stressors

- CPs and PAs: work pressuring (e.g. by prioritising dispensing of prescribed medicines, crowded waiting area) can lead to omitting WWHAM questions; consulting room or privacy counter should be offered when required (verbal or nonverbal signs); introduction of

background music if possible, screens between counters, measuring of voice volume, PAs listening in the waiting area to colleagues advising at the counter; language may be a problem, specially in areas with low-literacy patients, patients from different cultural backgrounds, e.g. refugee accommodations, or consumers on vacation; hurried consumers may refuse information or not be willing to answer questions; pharmacy image with GPs and patients that products are more expensive in pharmacy than at other OTC outlets.

- CPs: improvement of logistic processes can decrease number of patients in waiting area and increase time available for advice.
 - PAs: consumers react both positive and negative on consultation room offer.
-

Sub-theme: Organisational culture and climate

- CPs: important to create hospitable atmosphere and product display in waiting area to facilitate self-medication; PAs that switch to pharmacy from other professions are mainly trained on location, most of them having a high education level and being very motivated.
- PAs: pharmacist attaching importance to high level of patient care.

Sub-theme: Person environment interaction

- CPs: conversations running smoothly if people are open to it and ask questions; important to discuss what information from internet led a consumer to resolutely ask for a specific product after acknowledging the effort of searching for information; self-care medication incidentally discussed in pharmacotherapeutic meetings with GPs when relevant for chronic conditions, doubts about knowledge of GPs of self-care advice in pharmacy.
- PAs: patients needing a clear advice, no more than 2 options to choose from; if patients are hurried you should remain calm and ask required questions; if GP refers patient to pharmacy for self-care product, PA should ask what the GP told already; preventive behavioural advice only working if patient is prepared to listen.

Sub-theme: Resources and material resources

- CPs: use of www.apotheek.nl for patient information, most pharmacies no longer use brochures; access to patients' medication record; PO checklists; self-care guidelines; stickers for PO medicines and for OTC products interacting with chronic medication.

Sub-theme: Target audience

- CPs and PAs: mostly young childrens' parents and elderly patients asking advice, people in between mostly asking for a specific product; patients asked about purchase location of OTC medication during medication review consultations.
-

TDF domain: Social influences

Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours

Sub-theme: Social pressure

- CPs and PAs: pressure from outside (e.g. commercials, family, friends) that creates unrealistic expectations in consumers requiring to create confidence prior to the advising process; resistance from consumers if they do not understand the reason for PA's questions.

Sub-theme: Social support

- CPs and PAs: when PAs are insecure about advice they confer with one another before consulting the pharmacist, mostly in complex situations.
-

TDF domain: Emotion

A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event

Sub-theme: Positive/negative affect

- CPs: a consumer who is happy with the advice providing the pharmacist with a satisfied feeling; a pharmacist who trained PAs that switched jobs felt proud to offer them a high education level; disappointment when consumers are not open to preventive advice.
PAs: helping people gives a contented and nice feeling, especially when the consumer intends to follow up on advice.
-

TDF domain: Behavioural regulation

Anything aimed at managing or changing objectively observed or measured actions

Sub-theme: Feedback

- CPs: discussing results of knowledge and skills assessment important to identify opportunities for improvement; CP should take time to listen to PA advice and provide feedback in case of incorrect advice, either during or immediately after self-care consultation; CP can encourage PAs to share new insights or information, or to encourage trainees and starting PAs to listen to experienced PAs providing self-care advice.
 - PAs: discussing the number of dispensed PO products and the percentage of PO dispensings entered into the pharmacy information system and deciding on follow-up; positive feedback from patients after they followed up on advice stimulates CPs to continue paying attention to self-care advice.
-

CHAPTER 2.2

Allergic rhinitis self-care advice in community pharmacies: a simulated patient study

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Exploratory Research in Clinical and Social Pharmacy 4 (2021)
100086

<http://dx.doi.org/10.1016/j.rcsop.2021.100086>

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Abstract

Background

Pharmacists and pharmacy assistants can support consumers by identifying minor ailments and providing evidence-based advice about treatment options. In the Netherlands, advice is based on national minor ailment guidelines and structured WWHAM questions (Who, What, How long, Action, Medication).

Objectives

To study whether pharmacy assistants provide guideline-compliant advice for allergic rhinitis based on WWHAM and condition-specific questions (When and Familiarity) and their association with appropriate self-care advice.

Methods

A retrospective study of the assessments of simulated patient (SP) visits regarding one condition- and two symptom-based cases of allergic rhinitis in Dutch community pharmacies. Pharmacies that participated in 2014, 2016 and 2018 were selected. SPs documented their observations of the problem analysis, dispensing and client interaction on a standardized scoresheet. Dispensing of an oral antihistamine according to the guideline recommendation was considered as the correct outcome. Chi-square tests were used to analyze differences in scores for problem analysis of pharmacies with correct and incorrect advice provision in 2014 and 2018. Predictors for correct outcome were identified by logistic regression analysis.

Results

Data from 673 pharmacies were available for all three years. In 2014 and 2018, problems were presented as a symptom (running nose), and 41.2% and 21.1% of pharmacies dispensed an antihistamine. For the condition-based problem (allergy) in 2016, 96.0% of participating pharmacies dispensed an antihistamine. Both in 2014 and 2018, each additional problem analysis question increased the odds ratio of providing correct advice. Questions asked about 'hay fever symptoms', 'medication', 'when symptoms occurred', and 'familiar symptoms' were significant predictors of correct advice provision.

Conclusions

Most pharmacies provided appropriate advice for a condition-based request but less than half of them provided appropriate advice for a symptom-based request. More questions asked was associated with increased chance of providing correct advice. Addition of condition-specific questions may improve the WWHAM-method.

Introduction

The World Health Organisation (WHO) defines self-care as the ability of individuals, families and communities to promote health, prevent disease, maintain health and cope with illness and disability with or without support from a healthcare provider [1]. Pharmacists can support self-care for consumers with minor ailments such as allergic rhinitis by identifying conditions and providing evidence-based treatment options [2, 3].

The prevalence of confirmed allergic rhinitis in adults in Europe ranges from 17% to 28.5% [4]. Symptoms include nasal congestion, running nose, sneezing and itching of the nose, palate and/or eyes [4, 5]. In the Netherlands the allergic rhinitis self-care guideline as a first choice recommends an oral non-sedative oral antihistamine (e.g., cetirizine or loratadine) [6]. Nose sprays and eye drops with sodium cromoglycate are available without prescription but not recommended by the guideline. Ocular and nasal azelastine have only recently (2021) been reintroduced as nonprescription medicines after having been available only on prescription for a decade. Contrary to some other countries, in the Netherlands nasal corticosteroids for hay fever treatment are available only on prescription.

In the Netherlands, pharmacy assistants who have completed a three-year vocational program assist the pharmacist by advising consumers on the use of nonprescription medicines to treat minor ailments. Advising on nonprescription medicines and self-care conditions is part of the competence profile of pharmacy assistants, and pharmacy assistants are required to adhere to guidelines and provide their patients with up-to-date evidence-based treatment advice to ensure optimal health outcomes [7]. To analyze a patient's problem, pharmacy assistants and pharmacists are trained to ask WWHAM-questions (i.e., 'Who is it for', 'What are the symptoms', 'How long have the symptoms been present', 'Has any Action already been taken', 'Has any other Medication been taken'), according to national self-care guidelines [6]. The Allergic rhinitis guideline also recommends to ask the questions 'when symptoms occur' and 'whether symptoms are familiar': specific allergic rhinitis questions additional to the WWHAM-mnemonic.

Studies in the UK and Australia have shown that a higher number of problem analysis questions resulted in improved outcomes for minor ailment treatment

and supply of nonprescription medication [8-10]. A UK study also showed that individual WWHAM questions (e.g. description of symptoms and other medication) were predictors in addition to the total number of questions asked [9]. However, other studies in the UK have found that the use of questioning strategies such as WWHAM during problem analysis had limited impact on patient outcomes and that pharmacists were overly reliant on this type of questioning strategy [11, 12]. These findings suggest that the WWHAM protocol may be important but not always sufficient. Additional questions that may be relevant to a specific minor ailment should be asked; otherwise, crucial information for decision-making can be missed [13]. Furthermore, the pharmacy assistant should also accurately collect necessary information, followed by appropriate problem identification and final advice [14].

Dutch pharmacies have the opportunity to assess adherence to national self-care guidelines through simulated patient (SP) visits on a regular basis [15]. SPs are specifically trained actors who pretend to be regular consumers visiting the pharmacy for minor ailment advice. Pharmacies can use the results of the regular assessments to improve the quality of consultations on minor ailments.

The aim of this study was to investigate whether pharmacy assistants provide guidance-compliant advice for allergic rhinitis by studying (1) associations between quality of problem analysis (use of WWHAM and condition-specific questions) and guideline recommended advice for symptom-based requests in 2014 and 2018, (2) dispensing of nonprescription medication for a condition-based request in 2016 and (3) general communication skills (conversation skills and consumer interaction).

Methods

Setting

In the Netherlands, from 2014 to 2018 there were 1979 to 1996 community pharmacies [16, 17]. In 1995, AMP Research and Advice in Healthcare started using SP visits to assess self-care advice in Dutch community pharmacies [15]. Pharmacies voluntarily self-subscribe to the assessment program and pay a fee per year. Participating pharmacies are visited 4 times annually by a SP for a condition- or symptom-based self-care request. Subsequently, they receive an

extensive report of the assessment results, including a benchmark comparison with the national average, the highest-scoring pharmacy, and comparison with previous results of their pharmacy during the current year.

Design

This retrospective cross-sectional study examined SP visits for allergic rhinitis at community pharmacies in the Netherlands in 2014, 2016 and 2018. After drafting the research question, the AMP research team developed the scenario through review of guidelines [5, 18-20] and literature. A scenario script was developed including starting question, description of the condition, answers to anticipated questions and correct outcome. After discussion of the scenario script with a limited number of SPs, the scenario was tested in 10 pharmacies who did not subscribe to the program, and where needed the scenario script was adjusted. Table 1 shows case descriptions for all study years. Before the assessments in all subscribing pharmacies started, the final version of the scenario script was discussed with all SPs to ensure similar interpretation. In the pharmacy, the SPs asked their starting question when a pharmacy team member (pharmacy assistant or pharmacist) addressed them at the counter.

Table 1. Case descriptions

	2014	2016	2018
Type of case & question	Symptom-based: Something for a running nose	Condition-based: Something for allergy	Symptom-based: Something for a running nose
For Whom (W)	Simulated patient	Simulated patients' husband	Simulated patients' daughter aged 15 years
Additional symptoms (W)	Sneezing Itching of the nose Itching and tearing of the eyes Itching palate Sometimes nasal congestion	Allergy to cats Mainly sneezing and a running nose, sometimes itching and tearing of the eyes	Sneezing Itching of the nose Sometimes itching palate, earache, nasal congestion
How long (H)	A few weeks	Since babysitting at her daughter's house yesterday	Approximately 4 weeks
Action taken already (A)	No	No	No
Other medication (M)	No	Tamsulosin	No
When	More symptoms in the afternoon and in dry weather	In a house with a cat or other pets	Mainly when she's walking the dog and cycling to school, worse in dry weather. She got the Labradoodle, 6 months earlier. No complaints when playing with the dog
Familiar with symptoms	Yes, since relocation to her current house 2 years ago Does not feel like common cold	Yes, he had something from a pharmacy earlier	No, no previous symptoms Does not feel like common cold
Correct advice	Oral cetirizine or loratadine		
Incorrect advice	Other antihistamine Ocular sodium cromoglycate Nasal xylometazoline or xylometazoline/ipratropium Other products (nasal saline, herbal product) No product dispensed		

Data collection

The assessments were performed from 17 April–28 May 2014, 8 March–13 April 2016, and 8 March–11 April 2018, respectively. Only pharmacies that participated in all three assessments were selected to obtain results from comparable populations. The SPs recorded problem analysis questions, consultation characteristics, and general communication characteristics on a standardized data collection form in binary answers (yes or no), immediately after each visit. Recommended products were bought and noted in the data collection form. The data collection form was based on the Dutch self-care allergic rhinitis guideline and other relevant guidelines [5, 20]. All pharmacy visits were audio recorded. By default, AMP used these recordings to check the validity of the data collection form.

Data analysis

The number of participating pharmacies was 823 in 2014, 948 in 2016 and 934 in 2018. The number of pharmacies participating in all 3 years was 673. The results of all of these pharmacies were analyzed. A score of 1 point was allocated to each problem analysis question asked by the pharmacy assistant [9]. In 2014 and 2018, a chi-square test was used to analyze individual problem analysis questions for differences between pharmacies that did and did not provide correct advice ($p < 0.05$). The maximum total score for problem analysis, which consisted of WWHAM and 2 condition specific questions that are mentioned in the guideline, was 7. A chi-square test was used to analyze the total score for problem analysis and the median consultation time for differences between pharmacies that did and did not provide correct advice in 2014 and 2018, as well as between 2014 and 2018 ($p < 0.05$). Pharmacies with correctly and incorrectly advised medications were counted, and percentages of all pharmacies were calculated. A univariate logistic regression was performed to assess the association between total problem analysis score and correct advice provision in 2014 and 2018 ($p < 0.05$). A multivariate analysis with all individual questions was performed for 2014 and 2018 to further analyze the contribution of individual problem analysis questions ($p < 0.05$). For this analysis, specific questions about hay fever and common cold symptoms were used instead of the general question, 'Do you have any other symptoms?'. For 2014 and 2018, chi-square test was used to analyze differences in the general communication characteristics for pharmacies that

did and did not provide correct advice ($p < 0.05$).

All statistical analyses were performed using Statistical Package for the Social Sciences, IBM SPSS statistics for Windows, version 26.0.

Ethics

All data were anonymous and could not be traced back to the participating pharmacies. Use of routinely collected and anonymous observational data is not subject to the Medical Research Involving Human Subjects Act (WMO) in the Netherlands. Therefore, the study protocol did not need to be submitted for review by a medical ethics committee. All pharmacists participating in the assessment program have provided written consent to AMP to use the assessment data for research.

Results

Basic characteristics

A total of 673 pharmacies participated in all three years of data collection. Table 2 shows the basic characteristics of the consultations in these pharmacies. In the 2014 and 2018 symptom-based scenarios, the median consultation time in pharmacies that provided correct advice was significantly higher than in pharmacies that provided incorrect advice ($p < 0.05$); in the 2016 condition-based scenario, the difference in consultation time between correct and incorrect advice provision was not significant. In 2018, the consultation time was significantly higher than in 2014 for all pharmacies, including those that provided correct advice and those that provided incorrect advice ($p < 0.05$).

Table 2. Consultation characteristics of community pharmacies (n = 673)

	2014		2016		2018	
Median waiting time before consultation, minutes (min–max)	1.0	(0–29)	2.0	(0–25)	2.0	(0–26)
Median consultation time, minutes (min–max)	3.0	(1–19)	3.0	(1–20)	4.0	(1–34)
in pharmacies that provided correct advice	4.0	(1–19)	3.0	(1–20)	7.0	(1–34)
in pharmacies that provided incorrect advice	2.0	(1–13)	4.0	(1–10)	3.0	(1–15)
Separate self-care counter: n(%)	57	(8.5%)	43	(6.4%)	51	(7.6%)
Self-care advisor's job title visible on name plate: n(%)	80	(11.9%)	89	(13.2%)	109	(16.2%)
Consultation with a colleague: n(%)	85	(12.6%)	71	(10.5%)	137	(20.4%)
consultation with a pharmacist: n(%)	3	(0.5%)	13	(1.9%)	18	(2.7%)
Sufficient attention to privacy: n(%)	433	(64.3%)	470	(69.8%)	406	(60.3%)
Queuing system in waiting area: n(%)	113	(16.8%)	138	(20.5%)	140	(20.8%)

Symptom-based scenarios (2014 and 2018)

Of all pharmacies, 10.8% ($n = 73$) provided correct advice in both 2014 and 2018, and 48.4% ($n = 326$) provided incorrect advice in both years. Only 10.4% ($n = 70$) of all pharmacies that had provided incorrect advice in 2014, then provided correct advice in 2018. In 2014 and 2018, pharmacies that provided correct advice had significantly higher scores for all individual WWHAM problem analysis questions, as well as the condition specific questions regarding 'when symptoms occurred' and 'familiarity with symptoms', than pharmacies that provided incorrect advice ($p < 0.05$; see Table 3).

Table 3. Numbers (and percentages) of pharmacies that provided correct and incorrect advice and had a positive score on individual problem analysis questions

	2014		2016		2018	
	Correct	Incorrect	Correct	Incorrect	Correct	Incorrect
Year	2014		2016		2018	
Advice	Correct	Incorrect	Correct	Incorrect	Correct	Incorrect
Number of pharmacies	277	396	646	27	143	530
Who (W)	149 (53.8%)*	160 (40.4%)*	454 (70.3%)	17 (63.0%)	139 (97.2%)*	430 (81.1%)*
Symptoms, in general (W)	277 (100.0%)*	239 (60.4%)*	577 (89.3%)	26 (96.3%)	143 (100.0%)*	389 (73.4%)*
Symptoms of hay fever ^a	248 (89.5%)*	116 (29.3%)*	NA	NA	124 (86.7%)*	198 (37.6%)*
Symptoms of common cold ^b	114 (41.2%)	126 (31.8%)	NA	NA	76 (53.1%)*	207 (39.1%)*
Both hay fever and common cold	109 (39.4%)*	63 (15.9%)*	NA	NA	72 (50.3%)*	110 (20.8%)*
How long symptoms present (H)	177 (63.9%)*	121 (30.6%)*	153 (23.7%)	9 (33.3%)	111 (77.6%)*	230 (43.4%)*
Action taken (A)	155 (56.0%)*	134 (33.8%)*	464 (71.8%)	14 (51.9%)	106 (74.1%)*	257 (48.5%)*
Other medication (M)	213 (76.9%)*	151 (38.1%)*	460 (71.2%)	23 (85.2%)	121 (84.6%)*	222 (41.9%)*
When symptoms occur	109 (39.4%)*	47 (11.9%)*	167 (25.9%)	14 (14.8%)	92 (64.3%)*	92 (17.4%)*
Familiar symptoms	160 (61.0%)*	83 (21.0%)*	209 (32.4%)	1 (3.7%)	103 (72.0%)*	137 (25.8%)*

* statistical significance of difference between groups with and without correct advice, tested by chi-square ($p < 0.05$)

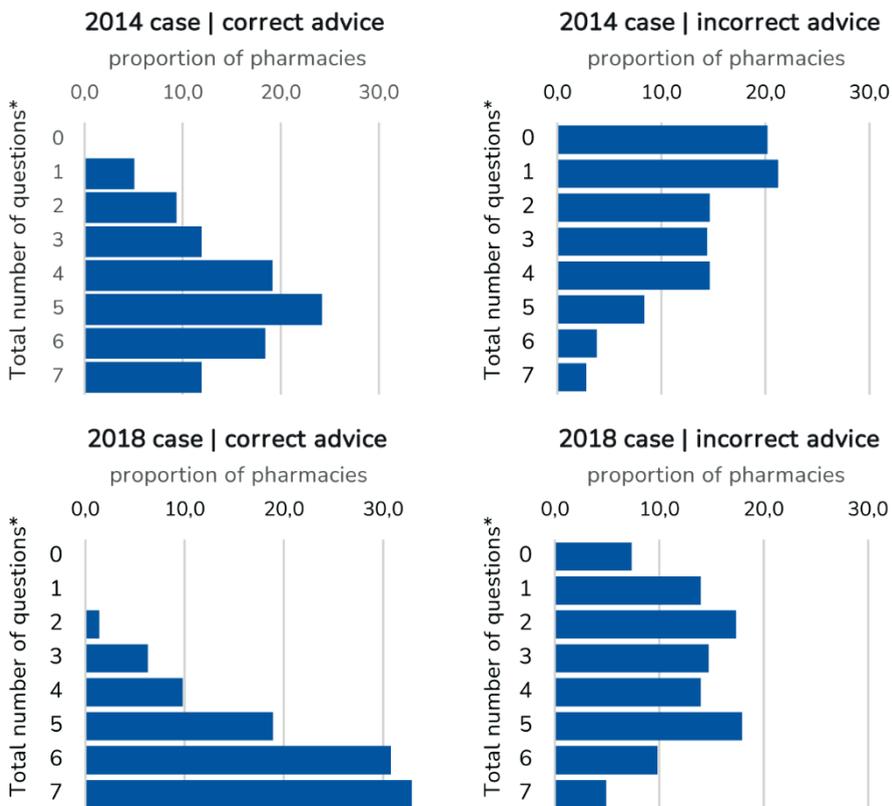
^a itching nose, sneezing, specification running nose, itching and tearing eyes, itching palate

^b stuffy nose, mucus appearance, sore throat, earache, elevated body temperature, fever or general malaise

Condition-based scenario (2016)

Table 3 shows that scores for individual problem analysis questions did not differ significantly for pharmacies that provided correct or incorrect advice. Questions about for whom the medication was meant for, action already taken and other medication used were asked by approximately 70% of pharmacy assistants. In the condition-based scenario 96.0% of all pharmacies advised an oral antihistamine according to the guideline, 2.5% advised sodium cromoglycate and almost 1% did not advise any product..

Figure 1: Percentages of pharmacies with correct and incorrect advice provision in 2014 and 2018 for total number of problem analysis questions (WWHAM plus condition-specific questions)



*WWHAM problem analysis questions

Figure 1 shows the total number of problem analysis questions asked at pharmacies in 2014 and 2018, including pharmacies that provided correct and

incorrect advice. In both years, the total number of questions asked in pharmacies that provided correct advice was significantly higher than that of pharmacies that provided incorrect advice ($p < 0.05$). In 2018, the total number of questions asked in pharmacies that provided correct advice was significantly higher than in 2014 ($p < 0.05$). The total number of questions asked in pharmacies that provided incorrect advice in 2018 was also significantly higher than in 2014 ($p < 0.05$). Both in 2014 and 2018, each additional problem analysis question significantly increased the odds ratio for providing correct advice, in 2014 with 1.8 (95% CI 1.7-2.0) and in 2018 with 2.3 (95% CI 1.9-2.6, see Table 4). Table 4 also shows the individual problem analysis questions that significantly increased the odds ratio of correct advice provision in 2014 and 2018. Asking about ‘when symptoms occur’ increased the odds ratio with 1.9 and 4.0 in 2014 and 2018 respectively; asking about ‘familiarity with symptoms’ increased the odds ratio with 2.4 and 2.6 in 2014 and 2018 respectively.

Table 4. Association between problem analysis questions and provision of a correct advice in 2014 and 2018

Problem analysis questions	Year	OR (95% CI)
All questions	2014	1.8 (1.7-2.0)
	2018	2.3 (1.9-2.6)
Hay fever symptoms	2014	2.8 (2.2-3.6)
	2018	1.5 (1.3-2.0)
Other medication	2014	2.4 (1.6-3.6)
	2018	3.9 (2.3-6.7)
When symptoms occur	2014	1.9 (1.2-3.0)
	2018	4.0 (2.5-6.3)
Familiarity with symptoms	2014	2.4 (1.6-3.0)
	2018	2.6 (1.6-4.2)

Table 5 shows the products (correct or incorrect according to the guideline) that were dispensed by pharmacies in each study year. The median number of problem analysis questions asked by pharmacy assistants who dispensed xylometazoline or xylometazoline/ipratropium in 2014 and 2018 was 1.5 and 2.0, respectively.

Table 5. Numbers (percentages) of all pharmacies for dispensed products in 2014, 2016 and 2018

Year	2014	2016	2018
Number of pharmacies	673	673	673
Products dispensed			
Correct advice:			
Antihistamine (cetirizine or loratadine)	277 (41.2%)	646 (96.0%)	143 (21.2%)
Incorrect advice:			
Sodium cromoglycate	72 (10.7%)	17 (2.5%)	72 (10.7%)
Xylometazoline	98 (14.6%)	0 (0.0%)	183 (27.2%)
Xylometazoline/ipratropium	192 (28.5%)	1 (0.1%)	126 (18.7%)
Other products (saline, herbal)	8 (1.1%)	3 (0.4%)	42 (6.2%)
No products dispensed	26 (3.9%)	6 (0.9%)	107 (15.9%)

General communication skills

Table 6 shows that almost all pharmacies consistently scored high on general communication skills and most SPs were content on being served. Both in 2014 and 2018, sufficient consulting time, contentment, repeating of agreements or actions, explicitly asking if everything was clear, and offering the possibility to contact the pharmacy for questions or persistent complaints were significantly higher for pharmacies that provided correct advice than for pharmacies that provided incorrect advice. For 2014, also appropriate ending of the conversation was significantly higher for pharmacies that provided correct advice.

Table 6. Percentages (numbers) of pharmacies for positive scores on communication characteristics, stratified for correct and incorrect advice

Advice	2014		2016		2018	
	Correct	Incorrect	Correct	Incorrect	Correct	Incorrect
Number of pharmacies	277	396	646	27	143	530
Friendly greeting	98.9 (274)	99.2 (393)	99.4 (642)	96.3 (26)	100.0(143)	99.6 (528)
Eye contact	100.0 (277)	99.2 (393)	99.4 (642)	92.6 (25)	99.3 (42)	99.4 (527)
Sufficient consulting time	99.6 (276)*	89.1 (353)*	97.8 (632)	96.3 (26)	100.0 (143)**	95.5 (506)**
Appropriate talking volume	98.2 (272)	97.5 (386)	96.3 (622)	92.6 (25)	97.9 (140)	97.2 (515)
No interruption from others	97.8 (271)	98.2 (389)	98.5 (636)	100.0 (27)	97.2 (139)	98.3 (521)
Appropriate language	99.6 (276)	100.0 (396)	100.0 (646)	100.0 (27)	99.3 (142)	99.6 (528)
Calm and clear voice	100.0 (277)	99.2 (393)	98.5 (636)	100.0 (27)	98.6 (141)	99.2 (526)
Confident appearance	96.8 (268)	94.7 (375)	98.9 (639)	96.3 (26)	97.0 (140)	96.8 (513)
Appropriate ending of the conversation	98.2 (272)*	91.2 (361)*	93.8 (606)	96.3 (26)	100.0 (143)	98.9 (524)
SP content on being served	98.9 (274)*	82.3 (326)*	99.1 (640)	85.2 (23)	100.0 (143)**	91.3 (484)**
Assistant repeats agreements or actions	66.4 (184)*	37.1 (147)*	36.2 (234)	51.9 (14)	80.4 (115)**	47.0 (249)**
Assistant explicitly asks if everything is clear/understood	65.3 (181)*	42.2 (168)*	58.7 (379)	55.6 (15)	44.1 (63)**	14.0 (74)**
Assistant mentions possibility to call or visit the pharmacy for questions or persistent complaints	25.3 (70)*	7.6 (30)*	23.1 (149)	25.9 (7)	50.3 (72)**	13.6(72)**

* statistical significance tested by Chi-Square test, difference significant if $p < 0.05$

** statistical significance tested by Chi-Square test, difference significant if $p < 0.05$

Discussion

Almost all pharmacies provided appropriate advice for a condition-based request (allergy) but less than half of all pharmacies gave appropriate advice for a symptom-based request (a running nose). In 2014 and 2018, the total number of questions and specific questions regarding the nature of the condition (e.g., asking about hay fever symptoms, other medications, when symptoms occurred and familiarity with symptoms) was associated with an odds ratio of 1.5–4.0 for providing correct advice. Most pharmacies scored consistently high on general communication skills like talking volume, appropriate language and eye contact. Pharmacy assistants that were insecure mostly consulted a colleague for advice; the percentage in 2018 being almost twice as high as in 2014 and 2016. Pharmacists were consulted by a very low percentage of pharmacy assistants.

The problem analysis questions were not consistently asked in pharmacies in 2014 or 2018. Within pharmacies, the probability of providing correct advice likely depended on the competency of the individual pharmacy assistant who provided the advice. The education level of pharmacy assistants in practice varies from a basic three-year vocational training to completed accredited (self-)care modules in addition to this basic training. In the Netherlands, the pharmacy technician position was added to the pharmacy workforce in 2004. To become a pharmacy technician, experienced pharmacy assistants must complete three additional years of training at the level of higher professional education, which includes theoretical courses and workplace learning [21]. An estimated 20–25% of the 2,000 community pharmacies in the Netherlands employ a pharmacy technician.

In 2014, 20% of pharmacy assistants asked no questions at all; this share was 7% in 2018. Possibly, feedback from earlier assessments may have led to more questions being asked. On the other hand, in 2018 there was no increase in the percentage of pharmacies that provided correct advice. In 2014 and 2018, pharmacy assistants in most pharmacies asked about symptoms in general. Also in 2014 and 2018, the majority of pharmacies that provided correct advice specifically asked about symptoms of hay fever; this share was significantly higher than that of pharmacies that provided incorrect advice. Itching symptoms distinguish hay fever from a common nose cold. Asking questions about these symptoms of hay fever at the beginning of a

consultation should increase the odds ratio of identifying the correct condition and reduce clinical consultation time [13]. Asking about 'when symptoms occur' and about 'familiarity of symptoms' significantly increased the odds of correct advice provision as well. Condition specific questions may be added to the WWHAM-method to encourage pharmacy assistants to ask these questions. In 2014 and 2018, also pharmacies that provided incorrect advice frequently asked about symptoms of hay fever; but in these pharmacies the condition specific questions did not lead them to provide correct advice. A reason might be that counselling follows a process of collection of relevant information, correct problem identification and adequate problem solving and advice [14]. This process can be supported by the WWHAM plus condition specific questions, but this may not be sufficient and additional skills may be needed.

Pharmacies use reports from SP visits as feedback to improve their counselling on minor ailments. Previous studies using SPs mostly included a limited number of pharmacies in a designated area [22-25]. This study analyzed data from a high number of pharmacies all over the country which offers insight into the quality of self-care advice on a national level. Each individual pharmacy SP visit provided a snapshot of a counseling situation; however, because of the large number of snapshots over time an overall picture of the counselling and advice quality during subsequent years could be collected. Earlier research of self-care scenarios of AMP in 2016 and 2017 (4 cases in each year) also found that problem analysis questions were not consistently asked in Dutch pharmacies [26]. Pharmacy assistants' relatively low adherence to counselling guidelines may reflect the low priority of advice for minor ailments in Dutch pharmacies; pharmaceutical care generally focusses on prescription related medication issues (e.g., dispensing information, drug shortages, and medication review) [27]. It is the pharmacist's responsibility to ensure that pharmacy assistants are competent self-care advisors. This competence requires ready knowledge of minor ailments and accurate appraisal of answers, on which items the pharmacy support workforce should be trained.

In the 2016 condition-based scenario, nearly all pharmacy assistants dispensed an appropriate product when the SP asked for something to treat an allergy, which suggests that they were aware of the guideline recommendation for allergic rhinitis. However, in the 2014 and 2018 symptom-based scenarios, less than 50% of pharmacies dispensed an

appropriate product according to the guideline. In 2014 and 2018, xylometazoline was dispensed by more than 40% of all pharmacies, likely because pharmacy assistants asked a low number of questions (median: 1.5 and 2.0, respectively) and concluded that the symptoms were caused by a common cold. The timing of SP visits may have been a factor that contributed to the assumption of a common cold [28].

These differences in performance are compliant with an overview of the simulated patient method which stated that scenario variation was shown to affect performance, including whether it relates to a direct product, a condition- or symptom-based request [29].

In 2016, the median consultation time among pharmacies that provided correct advice was about 25% lower than that of pharmacies that provided correct advice in 2014. Contrary to 2014, in 2016 allergic rhinitis did not need to be established because the SP presented with an allergy and a much lower median consultation time was expected. In 2016, only the WWHAM questions for whom the product was meant for, use of other medication and the condition specific question about the kind of allergy were relevant for correct advice provision. The higher than expected consultation time in 2016 may be caused by pharmacy assistants failing to distinguish between essential and non-essential questions. Notably, there was a wide range of consultation times in all years, including for pharmacies that provided correct and incorrect advice. If the right questions are asked and answers are interpreted appropriately, providing correct advice may not take a long time. However, training is necessary to acquire this competency.

Strengths and limitations

A strength of this study lies in the relatively large number of pharmacies included. The 673 participating pharmacies account for more than one-third of the total number of pharmacies in the Netherlands [27]. Moreover, the percentage of chain owned pharmacies in this study was 23% in 2016, whereas the national percentage of chain owned pharmacies in 2016 was 30% [27]. Therefore, the results are likely representative of all community pharmacies in the Netherlands. An additional strength is that pharmacy staff were not aware of when they were being assessed, the identity of the SP or the self-care case that was being assessed.

A potential limitation is that the included pharmacies participated in the AMP program more than once, which suggests that participating pharmacies may be more focused on long-term development of self-care advice than other pharmacies. Therefore, the findings may skew toward an overestimation of the quality of pharmacies. However, in all study years one of the largest healthcare insurance companies offered the 50% highest scoring pharmacies that participated in the program a higher dispensing fee. For pharmacists, this may have been the incentive to subscribe to the program.

Only limited percentages of pharmacy assistants consulted a colleague or pharmacist. There may have been instances that the SP interacted with a pharmacist and not a pharmacy assistant. However, a complete account of the number of staff members that referred to a pharmacist could not be determined, as not all staff wear a pharmacy name plate.

This study compared the symptom-based scenarios in 2014 and 2018 despite of differences in the scenarios, for example, the SP's age and familiarity with symptoms. Overall the 2018 scenario may have been more difficult than the 2014 scenario which may have contributed to the lower scores for correct advice provision. Also, the pharmacy assistants that approached the SP in 2014 and 2018 may have been different persons. This may as well have resulted in different scores for correct advice provision.

Implications for practice

The study findings indicate that pharmacists should ensure that their pharmacy assistants have ready knowledge of minor ailments and are able to accurately appraise the answers they receive (e.g., through training) and should work to implement a pharmacy-wide self-care counselling policy to reduce the variety of advice given by different team members. Team discussions of the results of SP visits may be an adequate instrument to achieve these goals. With their team they can also discuss the recommendations of the guideline including condition-specific questions, instead of solely focusing on the WWHAM-mnemonic. Implementation of these actions may lead to the provision of consistent evidence-based advice, possibly with a reduction in consultation time. Pharmacists can also discuss with their team the point at which pharmacy assistants should consult them for self-care questions regarding allergic rhinitis.

Management of allergic rhinitis is a complex process that requires a

coordinated effort from consumers, patients and healthcare providers, including pharmacists and pharmacy assistants [30]. A self-care counselling policy may benefit from the input of local GPs, based on a recent study finding that approximately 15–40% of people with allergic rhinitis also suffer from asthma and 80–90% of asthmatic patients also suffer from allergic rhinitis [31]. Agreements can be made with GPs regarding referral of pharmacy clients to the GP practice.

Conclusions

The study findings indicate that a more detailed problem analysis by a pharmacy assistant is associated with an increase of the odds ratio of providing correct advice for a minor ailment. In 2014 and 2018, condition specific questions were also associated with an increase of the odds ratio of providing correct advice. In 2016, nearly all pharmacies dispensed an antihistamine for allergy when the patient specifically stated that they had a (pet) allergy. In 2014 and 2018, only half of the questions that predicted correct advice provision were part of the WWHAM mnemonic. Therefore, adding condition-specific problem analysis questions to the WWHAM mnemonic may be considered alongside educating the pharmacy team in ready knowledge and accurate appraisal of answers to questions asked, although ready knowledge and accurate appraisal were not specifically assessed in this study. Most pharmacies scored consistently high on conversation characteristics like talking volume, appropriate language and eye contact.

Acknowledgements

The authors thank pharmacist Hetty Prins and AMP researcher Martijn Hendrix for providing the data for this study, as well as Valerie Kleuver for her work on this study in the context of her master's research.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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CHAPTER 3

Treatment and prevention of (recurring) urinary tract infection in the Netherlands



CHAPTER 3.1

Adherence to guideline
recommendations for urinary tract
infections in adult women, a cross-
sectional study

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Primary Health Care Research & Development 22(e11): 1-8

<http://dx.doi.org/10.1017/S1463423621000116>

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Abstract

Aim

To study whether changes in drug preferences in the Dutch guideline for the treatment of Urinary Tract Infection (UTI) for General Practitioners in 2013, resulted in corresponding changes in antibiotic dispensing.

Background

For the treatment of uncomplicated UTI, nitrofurantoin remained the first choice, while fosfomycin became the second choice and changed ranks with trimethoprim. For a subsequent febrile UTI, ciprofloxacin became the first choice and changed ranks with amoxicillin/clavulanic acid, co-trimoxazole remained the third choice.

Methods

In this observational cross-sectional study, routinely collected dispensing data from the Dutch Foundation of Pharmaceutical Statistics from 2012 to 2017 were used. Numbers of women 18 years and older, treated with one of the guideline antibiotics for uncomplicated UTI and subsequent febrile UTI were analysed annually. Proportions were calculated. Data were stratified for age categories. Failure of uncomplicated UTI treatment was defined as the dispensing of an antibiotic for febrile UTI within 14 days after the dispensing of an antibiotic.

Findings

Data were available from 81% of all pharmacies in 2012 to 89% in 2017. Percentages of women dispensed nitrofurantoin were relatively stable with 87.4% in 2012 and 84.4% in 2017. Percentages of women dispensed fosfomycin increased from 5.4% in 2012 to 21.8% in 2017, whereas percentages of women dispensed trimethoprim decreased from 17.8% to 8.0%. Within age categories, the percentage of women dispensed fosfomycin increased from 12.4% in women 18 – 30 years old to 36.7% in women above 80 years old. Percentages of women dispensed antibiotics for febrile UTI remained stable at 5% annually. Percentages of women receiving ciprofloxacin increased from 1.9% in 2012 to 3.3% in 2017, while those receiving amoxicillin/clavulanic acid decreased from 2.9% to 1.8%. New guideline recommendations resulted in corresponding changes in dispensed antibiotics for uncomplicated UTI and subsequent febrile UTI. Drug choices differed for age categories.

Introduction

In primary care, the most common acute presentation in women is uncomplicated Urinary Tract Infection (UTI) [1]. Every second woman experiences uncomplicated UTI at least once in her lifetime [1]. In 2016, in the Netherlands the prevalence of uncomplicated UTI in women was 103.5 per 1000 patient years. The Dutch guideline for General Practitioners (GPs) for UTI treatment (2013) recommended the following antibiotics for treatment of uncomplicated UTI: nitrofurantoin as the first choice, fosfomycin as the second choice, and trimethoprim as the third choice [2]. In this guideline, fosfomycin and trimethoprim changed ranks compared to the preceding 2005 GP guideline. This change was supported by the high in vitro susceptibility of UTI pathogens to fosfomycin, the lack of cross-resistance between fosfomycin and other antibiotics [3], and the relatively high prevalence of bacterial resistance to trimethoprim [4]. If the response to the first guideline antibiotic for uncomplicated UTI is insufficient, the guideline recommends to start treatment with a second guideline antibiotic for uncomplicated UTI. A recent study in 15 European countries showed that as many as 12 unique antibiotics were listed as first-line empirical treatment options for uncomplicated UTI [5]. Nitrofurantoin was the most frequently recommended antibiotic for female patients with this indication and was listed as a first-line option for uncomplicated UTI in 12 of 15 guidelines, followed by fosfomycin and pivmecillinam.

If an episode of uncomplicated UTI develops into a febrile UTI, the 2013 Dutch guideline advised ciprofloxacin as first choice, amoxicillin/clavulanic acid as second choice, and co-trimoxazole as third choice. Compared to the preceding guideline, amoxicillin/clavulanic acid and ciprofloxacin changed ranks because of lower bacterial resistance to ciprofloxacin when compared to both amoxicillin/clavulanic acid and co-trimoxazole [4].

After revisions, new guideline recommendations must be implemented into clinical daily practice, which may take some time, as exemplified by a study in the United States (US) [6]. There, nitrofurantoin, fosfomycin, and trimethoprim-sulfamethoxazole were first-line antibiotics for uncomplicated UTI treatment according to a 2010 guideline [7]. For 2013, the US study showed that fosfomycin was prescribed for uncomplicated UTI in <0.01% of all visits and

almost half of antibiotic prescriptions were for non-guideline-recommended antibiotics [6]. Qualitative research showed unfamiliarity with fosfomycin as a possible first-line treatment option, along with the belief that fluoroquinolones achieve more rapid and effective control as the most important causes for GPs to ignore guideline recommendations [8]. Accordingly, in the UK, Clinical Commissioning Groups failed to implement into GP practice the change of nitrofurantoin from second to first choice and trimethoprim from first to second choice in uncomplicated UTI treatment [9].

This study aims to describe whether changes in drug preferences in the 2013 revision of the Dutch guideline of UTI for GPs, resulted in corresponding changes in drug choices, based on dispensing data for adult women in the Netherlands (2012 – 2017).

Methods

Design

An observational cross-sectional study was performed per calendar year (2012 – 2017) with routinely collected dispensing data from community pharmacies in the Netherlands.

Setting

In the Netherlands, antibiotics are only available through prescription. UTI is mainly treated in primary care. Overall, GPs in the Netherlands prescribe electronically, and their information systems offer electronic prescribing advice according to current GP guideline recommendations [10]. Prescriptions from GPs are sent electronically to community pharmacists. Most patients in the Netherlands visit one community pharmacy; consequently, pharmacists have complete virtual dispensing information for individual patients at their disposal [11].

Data source

Dispensing data were available from the Dutch Foundation of Pharmaceutical statistics (SFK) [12]. SFK routinely collects dispensing data from over 90% of all community pharmacies in the Netherlands. The total number of community pharmacies in the Netherlands was 1981 in 2012 and 1989 in 2017. SFK data cover GP prescriptions and outpatient prescriptions from medical specialists.

The data provided detailed information on the type and number of dispensings, the total amount of Defined Daily Dose (DDD) dispensed per year [13], and information about the prescriber (GP or medical specialist). Drugs were coded by the Anatomic Therapeutic Chemical Classification system (ATC) [13]. Information on patients' sex and year of birth were also available. The data did not contain information on clinical diagnoses. SFK data were coded and not traceable by the researchers to individual patients or pharmacies. During the research period for each calendar year, data were used from those community pharmacies that had provided complete data throughout the year.

Analysis

In each calendar year from 2012 to 2017, all women, 18 years and older, with at least one dispensing of the uncomplicated UTI guideline drugs nitrofurantoin (ATC code: J01XE01), fosfomycin (J01XX01), or trimethoprim (J01EA01), were counted. For these women, information was retrieved about their age, the prescriber of the antibiotic (GP or other prescriber), presence of a first dispensing in the corresponding year (defined as no dispensing of the same drug during the preceding 12 months), and at least one dispensing of an antibiotic for febrile UTI prescribed within 14 days after a dispensing of a guideline antibiotic for uncomplicated UTI. Numbers of women were counted annually for antibiotic use in uncomplicated or complicated UTIs. To enable comparison between calendar years, for each year, patient numbers from the included pharmacies were extrapolated to the total number of Dutch community pharmacies in that calendar year. Proportions were calculated for the users of individual antibiotics within all users of one of the UTI guideline antibiotics. User numbers were stratified for women with a first dispensing of one of the uncomplicated UTI guideline drugs, the GP as initiating prescriber, and women with a subsequent treatment course for febrile UTI. To provide more detailed insight into treatment choices for age categories, subanalyses were performed for 2017 (the most recent year). Proportions were calculated as descriptive statistics. Data were analysed with SPSS software, version 23 (SPSS Inc., Chicago, IL, USA).

Results

In 2012, data were available from 1608 community pharmacies (81% of all community pharmacies in the Netherlands) up to 1765 community pharmacies in 2017 (89% of all pharmacies). Our evaluation for 2012 showed that 743,692 women, 18 years and older, received at least one of three antibiotics recommended in the 2013 GP guideline for uncomplicated UTI treatment (Table 1). This number continuously increased to 787,214 women in 2017.

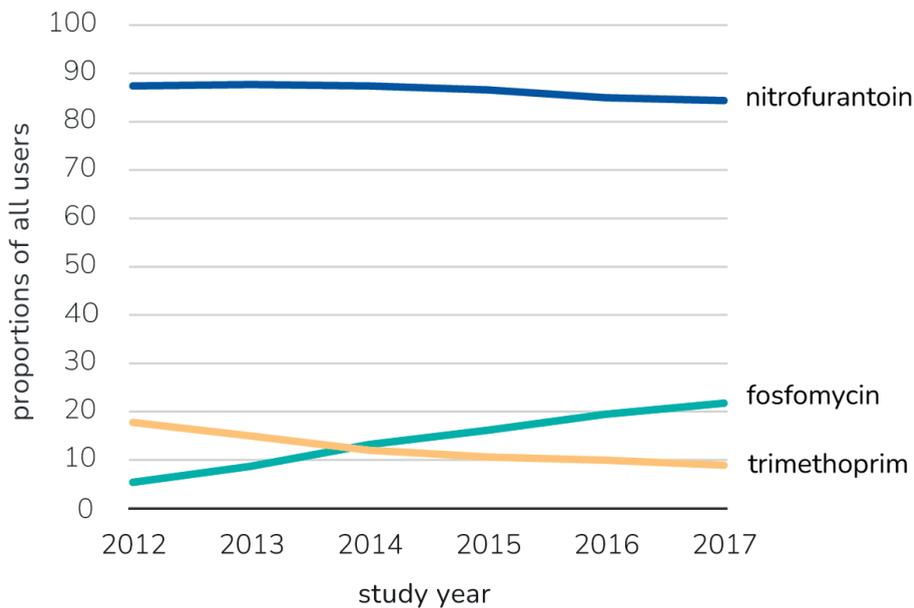
Table 1. Guideline preferred drugs for treatment of uncomplicated urinary tract infection in women ≥ 18 years between 2012 and 2017

Year	2012	2013	2014	2015	2016	2017
User numbers# of at least one uncompl UTI antibiotic (=N)	743,692 (100%)##	747,879 (100%)	767,122 (100%)	769,125 (100%)	774,822 (100%)	787,214 (100%)
nitrofurantoin (% of N)	650,337 (87.4%)	665,770 (87.7%)	670,182 (87.4%)	666,427 (86.6%)	658,898 (85.0%)	664,732 (84.4%)
fosfomycin (% of N)	40,187 (5.4%)	64,831 (8.7%)	101,151 (13.2%)	124,457 (16.2%)	150,812 (19.5%)	171,327 (21.8%)
trimethoprim (% of N)	132,269 (17.8%)	112,206 (15.0%)	91,812 (12.0%)	81,415 (10.6%)	77,250 (10.0%)	69,766 (8.9%)
Number of starters of at least one uncompl UTI antibiotic (=n)	635,078 (100%)##	643,329 (100%)	661,315 (100%)	666,381 (100%)	676,710 (100%)	692,741 (100%)
nitrofurantoin (% of n)	497,851 (78.4%)	501,208 (77.9%)	507,610 (76.8%)	503,853 (75.6%)	496,786 (73.4%)	506,344 (73.1%)
fosfomycin (% of n)	33,034 (5.2%)	54,889 (8.5%)	83,073 (12.6%)	100,042 (15.0%)	120,150 (17.8%)	133,304 (19.2%)
trimethoprim (% of n)	104,193 (16.4%)	87,227 (13.6%)	70,632 (10.7%)	62,486 (9.4%)	59,774 (8.8%)	53,093 (7.7%)
User numbers## of at least one febrile UTI antibiotic within 14 days (% of N)	39,099 (5.3%)	38,580 (5.2%)	41,018 (5.3%)	41,018 (5.3%)	41,238 (5.3%)	41,688 (5.3%)
ciprofloxacin (% of N)	14,242 (1.9%)	17,103 (2.3%)	23,145 (3.0%)	24,293 (3.2%)	25,016 (3.2%)	26,287 (3.3%)
amoxicillin/clavulanic acid (% of N)	21,878 (2.9%)	19,280 (2.6%)	15,976 (2.1%)	15,521 (2.0%)	15,103 (1.9%)	14,086 (1.8%)
co-trimoxazole (% of N)	5,237 (0.7%)	4,434 (0.6%)	3,520 (0.5%)	3,510 (0.5%)	3,424 (0.4%)	3,650 (0.5%)

The number of users was extrapolated to numbers of all community pharmacies in the Netherlands within the corresponding calendar year; In 2012 data were available from 1608 community pharmacies (81% of all community pharmacies), in 2013 from 1681 (85% of all community pharmacies), in 2014 from 1732 (88% of all community pharmacies) in 2015 from 1774 (90% of all community pharmacies) , in 2016 from 1806 (91% of all community pharmacies) and in 2017 from 1765 community pharmacies (89% of all community pharmacies)
 ##The sum of users of all guideline drugs per year is higher than 100% due to patients with more than 1 type of guideline drug per year

Figure 1 shows that the percentage of women with a dispensing for nitrofurantoin within all users of uncomplicated UTI antibiotics was relatively stable with 87.4% (n=650,337) in 2012 and 84.4% (n=664,732) in 2017. The percentage of women with a dispensing for fosfomycin increased from 5.4% (n=40,187) in 2012 to 21.8% (n=171,327) in 2017. Simultaneously, the percentage of women receiving trimethoprim decreased from 17.8% (n=132,269) in 2012 to 8.9% (n=69,766) in 2017.

Figure 1. Proportions^a of women ≥18 years with guideline antibiotics for Acute Cystitis^b between 2012 and 2017



^a Numbers available were extrapolated annually to all community pharmacies in the Netherlands within the corresponding calendar year and user proportions for a specific antibiotic were calculated among all users of AC antibiotics. In 2012 data were available from 1,608 community

pharmacies (81% of all community pharmacies), in 2013 data from 1,681 pharmacies (85% of all community pharmacies), in 2014 data from 1732 pharmacies (88% of all community pharmacies) in 2015 data from 1774 pharmacies (90% of all community pharmacies) , in 2016 data from 1806 pharmacies (91% of all community pharmacies) and in 2017 data from 1765 pharmacies (89% of all community pharmacies)

^h nitrofurantoin (1st choice in 2012 and 2017), fosfomycin (3rd choice in 2012, 2nd choice in 2017), trimethoprim (2nd choice in 2012, 3rd choice in 2017)

^r The sum of the proportions of the individual AC antibiotics per year was higher than 100% due to patients who used more than one type of AC guideline antibiotic within one calendar year.

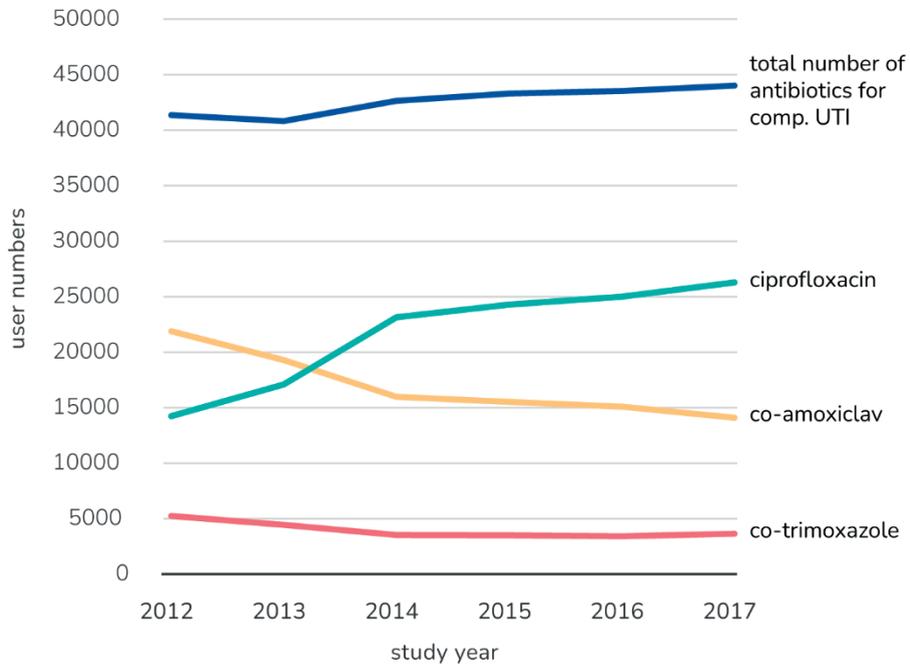
The number of women with dispensings of fosfomycin steadily increased annually from 40,187 in 2012 to 101,151 in 2017. In 2013 the user number increased to 64,831, twice the increase from 2011 to 2012. In 2014 the user number increased to 101,151 and in 2015 the user number increased to 124,457.

Percentages of starters with any of the three guideline antibiotics were between 85.4 % in 2012 and 88.0% in 2017. Within starters, percentages for those with a GP-prescription were quite stable between 90.4% in 2015 and 91.8% in 2013. Most frequently, nitrofurantoin was chosen in initial UTI treatment. Percentages of starters with this drug within all starters of UTI drugs slightly decreased from 78.4% in 2012 to 73.1% in 2017. Within age groups, percentages of starters with nitrofurantoin within starters of all UTI guideline drugs were highest for women between 18 and 30 years (89.2%) and lowest in the age category 81 years or older (66.4%, Table 2).

Percentages of starters with fosfomycin within all starters increased from 5.2% in 2012 up to 19.2% in 2017. Percentages of starters with fosfomycin were lowest with 12.7% in the age category 18-30 years and highest with 36.2% in the category 81 years and older.

Percentages of women with a dispensing for an antibiotic to treat febrile UTI within 14 days after an uncomplicated UTI antibiotic remained stable, remaining at 5.6% throughout the study period (Figure 2.) Use of amoxicillin/clavulanic acid declined during the study period (2.9% in 2012 to 1.8% in 2017), whereas the use of ciprofloxacin increased from 1.9% in 2012 to 3.3% in 2017. The use of co-trimoxazole was relatively stable, with 0.7% in 2012 and 0.5% in 2017.

Figure 2. User numbers of guideline antibiotics\$ for complicated UTI% within 14 days after a first, second or third choice guideline antibiotic for acute cystitis in women ≥18 years, between 2012 and 2017#



The number of users was extrapolated to numbers users of all community pharmacies in the Netherlands within the corresponding calendar year; In 2012 data were available from 1,608 community pharmacies (81% of all community pharmacies), in 2013 data from 1,681 pharmacies (85% of all community pharmacies), in 2014 data from 1732 pharmacies (88% of all community pharmacies) in 2015 data from 1774 pharmacies (90% of all community pharmacies) , in 2016 data from 1806 pharmacies (91% of all community pharmacies) and in 2017 data from 1765 pharmacies (89% of all community pharmacies)

\$ nitrofurantoin, fosfomycin or trimethoprim

% ciprofloxacin (1st choice in 2017), amoxicillin/clavulanic acid (2nd choice in 2017) or co-trimoxazole (3rd choice in 2017)

Table 2. Choice of guideline drugs for uncomplicated urinary tract infection in 2017 stratified for age category

Age category	18-30	31-40	41-50	51-60	61-70	71-80	>80
Users# of: at least one uncompl UTI antibiotic (=N)	142,771##	89,001	96,547	116,924	123,627	114,818	103,525
nitrofurantoin (% of N)	129,933 (91.0%)	80,147 (90.1%)	84,504 (78.4%)	99,740 (85.3%)	102,362 (82.8%)	91,653 (79.8%)	76,393 (73.8%)
fosfomycin (% of N)	17,880 (12.5%)	11,782 (13.2%)	16,460 (15.3%)	23,729 (20.3%)	29,954 (24.4%)	33,687 (29.3%)	37,948 (36.7%)
Trimethoprim (% of N)	6,873 (4.8%)	5,044 (5.7%)	6,798 (6.3%)	9,467 (8.1%)	12,323 (10.0%)	13,852 (12.1%)	15,409 (14.9%)
Starters### of: at least one uncompl UTI antibiotic (=n)	120,901##	75,112	79,312	93,305	95,309	85,457	74,984
nitrofurantoin (% of n)	107,843 (89.2%)	66,102 (88.0%)	67,562 (85.2%)	76,841 (82.4%)	75,077 (78.8%)	63,163 (73.9%)	49,776 (66.4%)
fosfomycin (% of n)	15,403 (12.7%)	10,139 (13.5%)	13,641 (17.2%)	19,012 (20.4%)	23,059 (24.2%)	24,925 (29.2%)	27,125 (36.2%)
trimethoprim (% of n)	5,888 (4.9%)	4,199 (5.6%)	5,415 (6.8%)	7,414 (7.9%)	9,314 (9.8%)	10,031 (11.7%)	10,834 (14.4%)
Users# of: at least one febrile UTI antibiotic within 14 days (% of N)	3,586 (2.5%)##	2,747 (3.1%)	3,559 (3.7%)	5,382 (4.6%)	7,128 (5.8%)	8,480 (7.4%)	10,806 (10.4%)
ciprofloxacin (% of N)	2,026 (1.4%)	1,509 (1.7%)	2,277 (2.4%)	3,497 (3.0%)	4,460 (3.8%)	5,502 (4.8%)	6,817 (6.6%)
amoxicillin/clavulanic acid (% of N)	1,448 (1.0%)	1,110 (1.2%)	1,075 (1.1%)	1,596 (1.4%)	2,168 (1.8%)	2,714 (2.4%)	3,976 (3.8%)
co-trimoxazole (% of N)	242 (0.2%)	211 (0.2%)	339 (0.4%)	515 (0.4%)	645 (0.5%)	810 (0.7%)	888 (0.9%)

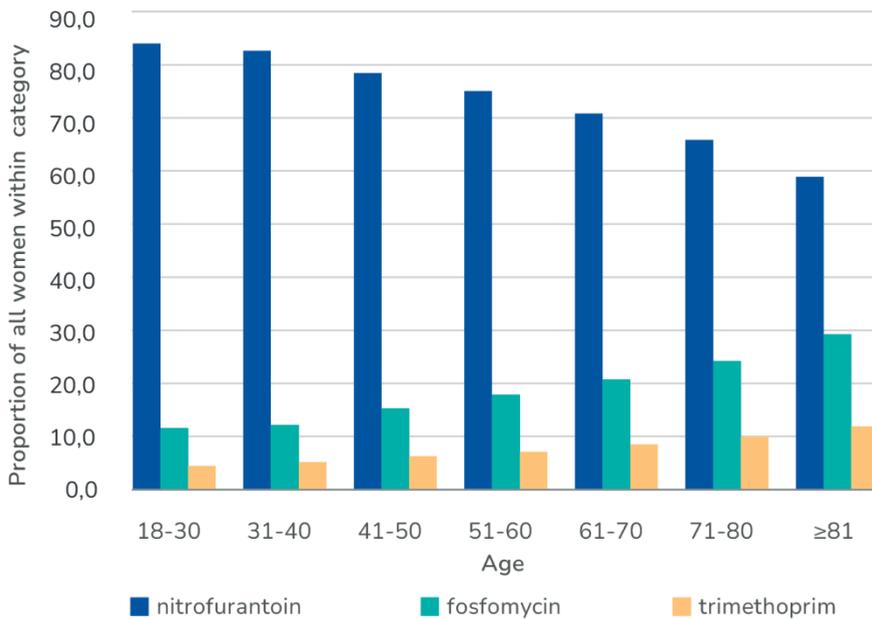
The number of users was extrapolated to the number of all community pharmacies in the Netherlands in 2017: in 2017 data were available from 1765 community pharmacies (89% of all community pharmacies)

##The sum of users of all guideline drugs per year is higher than 100% due to patients with more than 1 type of guideline drug per year

no dispensing of the same drug within the preceding 12 months

Figure 3 shows the users of uncomplicated UTI antibiotics in 2017, stratified for age categories. Within the two youngest age categories, from 18 – 30 and 31 – 40 years old, dispensing of nitrofurantoin was highest (91.0 and 90.1% respectively), whereas within the oldest age category (> 80 years old), only 73.8% were dispensed nitrofurantoin. Fosfomycin dispensings increased from 12.4% in the youngest age category to 36.7% in the oldest age category. Trimethoprim dispensings increased from 4.8% in the youngest age category to 14.9% in the oldest age category.

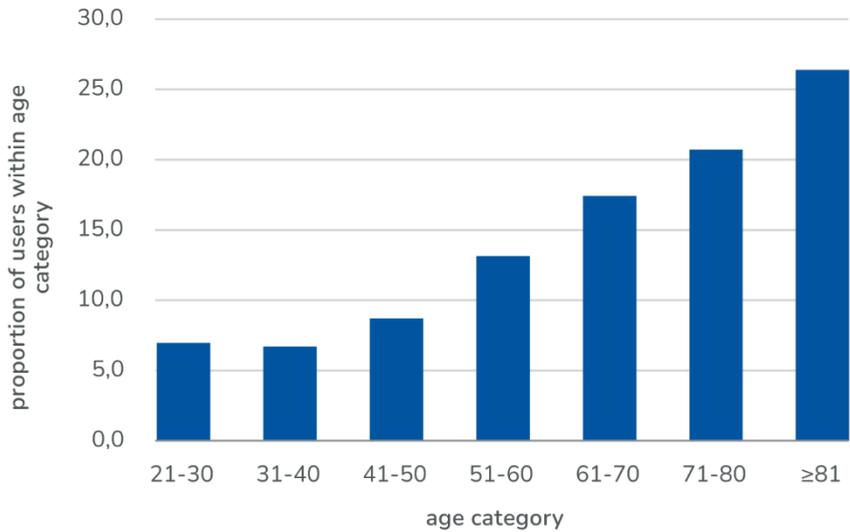
Figure 3. Percentages of users of the first, second and third choice guideline antibiotics for acute cystitis treatment^a in women ≥18 years, stratified for age categories in 2017



For annual user proportions user numbers from participating community pharmacies were extrapolated to all community pharmacies in the Netherlands in 2017: in 2017 data were available from 1765 community pharmacies (89% of all community pharmacies)

^a nitrofurantoin, fosfomycin or trimethoprim

Figure 4. Proportions of women with guideline antibiotics for complicated Urinary Tract Infection^h within 14 days after a guideline antibiotic for Acute Cystitisⁱ, stratified for age categories in 2017



^a Numbers available were extrapolated to all community pharmacies in the Netherlands in 2017 and user proportions were calculated among all users of complicated AC antibiotics within age categories. In 2017 data were available from 1765 community pharmacies (89% of all community pharmacies)

^h ciprofloxacin, amoxicillin/clavulanic acid or co-trimoxazole

ⁱ nitrofurantoin, fosfomycin or trimethoprim

Proportions of women who received an antibiotic dispensing for febrile UTI within 14 days after an uncomplicated UTI antibiotic also increased with older age (Figure 4). In the oldest age category, the use of ciprofloxacin was highest at 6.6% of all users, followed by 3.8% that were treated with amoxicillin/clavulanic acid. In women between 18 and 30 years old, dispensing for febrile UTI was lowest; 1.4% of these women was treated with ciprofloxacin and 1.0% with amoxicillin/clavulanic acid.

Discussion

The changes in recommendations for the drug preference in treating UTI within the GP guideline in 2013 showed corresponding changes in dispensing data. This was mainly pronounced in women receiving fosfomycin which became drug of second choice in the revised guideline. Corresponding to the new guideline recommendations, increased use of fosfomycin was mainly at the expense of trimethoprim, which had changed ranks with fosfomycin. Nitrofurantoin, which remained the first choice antibiotic in the guideline update, was the most preferred antibiotic for uncomplicated UTI.

In 2013 the user number of fosfomycin increased with 61.3% to 64,831, twice the increase from 2011 to 2012. In 2014 the increase in the user number of fosfomycin was 56%, but in 2015 the increase of the user number was lower with 23%. The use of fosfomycin was already increasing before the 2013 review of the guideline. According to SFK (oral communication), the user number of fosfomycin in 2008 was 14,928, which increased, with 20-30% yearly, to 40,187 in 2012. This is not surprising as guidelines often follow what is actually already happening in practice. There were already reports that showed increasing antibiotic resistance against trimethoprim and physicians started to prescribe fosfomycin when literature reviews suggested its effectiveness. Inclusion in the guideline as the second choice however, gave the final boost not only relatively, but also in the absolute number of fosfomycin users. Because the increase in 2013, the revision year of the guideline, and also that in 2014 were twice the increase in 2012 and in the years before, we regarded this increase as caused by the changes in the guideline.

For subsequent antibiotic treatment in febrile UTI, ciprofloxacin use increased as the newly advised first choice at the expense of amoxicillin/ clavulanic acid dispensings. Proportions of women with an antibiotic for febrile UTI within 14 days after an uncomplicated UTI guideline antibiotic were low. Moreover, the proportion of women in whom treatment for unresponsive UTI was started remained stable over the study period. Thus the increased use of fosfomycin did not seem to imply more subsequent antibiotic UTI treatment compared to nitrofurantoin or trimethoprim, suggesting a comparable effectiveness. However, more research may be needed to unambiguously determine the

effectiveness of fosfomycin in UTI treatment as a 5-day nitrofurantoin course for uncomplicated UTI treatment was shown to lead to a better cure after 28 days of follow up compared to a single dose of fosfomycin [14-17]. Nitrofurantoin remained the first choice because it causes less bacterial resistance compared to other antibiotics. In the Netherlands, in 2017, resistance levels of E Coli for nitrofurantoin and fosfomycin in selected GP patients were below 2% vs 24% for trimethoprim [18]. Resistance may be underestimated in GP practice, since cultures are usually only performed after failure of initial therapy or for a febrile UTI. Moreover, there is a concern of increasing resistance for fosfomycin with widespread use. A study in Israel showed an increase of fosfomycin resistance levels of E.Coli from 20.7% in 2015 to 30.9% in 2016; and of 17.6% in patients 51 years and younger versus 30.0% in older patients [19]. Consequently, the effectiveness of fosfomycin in UTI treatment has to be monitored further.

A recent review stated that in postmenopausal women, the choice of UTI antibiotics should involve efficacy, underlying patient health conditions, and side effects [20]. Nitrofurantoin is an appropriate first-line agent with known efficacy and minimal potential for collateral damage. Although nitrofurantoin remained the most dispensed antibiotic for all age categories, the proportions of nitrofurantoin users were lower in the older age categories, with higher proportions using fosfomycin and – to a lesser extent - trimethoprim. From dispensing data, we cannot elucidate the prescribers' considerations for a higher preference of fosfomycin and trimethoprim in older age categories. Possibly, prescribers preferred the ease of use of a single dose uncomplicated UTI treatment such as fosfomycin because of easier compliance in a population with potentially more drugs with chronic usage [20, 21]. Another reason for choosing an alternative to nitrofurantoin may have been drug shortages, which in the Netherlands for sustained-release nitrofurantoin have occurred, at least for a limited number of months in 2013, 2015 and 2017 [22]. Although direct release nitrofurantoin always was available, this alternative needs four daily dosages. This dosage regimen may hamper adherence, especially in cognitively impaired elderly patients, and may have further stimulated switching to the more user friendly one-off fosfomycin daily regimen. Prescribers may have also chosen to avoid nitrofurantoin in elderly patients as nitrofurantoin is contraindicated with impaired renal function. According to a

number of studies, this is only the case in seriously impaired renal function (eGFR < 30 mL/min) [23, 24]. A recent study, however, showed that in eGFR > 60 mL/min treatment with fosfomycin or trimethoprim for uncomplicated UTI was associated with more clinical failure than treatment with nitrofurantoin, while in eGFR < 60 mL/min nitrofurantoin was associated with more clinical failure than fosfomycin. Accordingly, renal function, if known, could be considered in the clinical decision-making for uncomplicated UTI treatment [25].

The number of women, 18 years and older, with uncomplicated UTI in absolute terms increased between 2012 and 2017, but the increase can most likely be attributed to demographic developments. The total number of all women in the Netherlands in 2012 was 8,447,477, which increased with 158,928 up to 2017. During these years the mean age increased from 41.5 to 42.5 years [26]. We hypothesize that this slight increase can be attributed to the ageing of the female population and the fact that older women more frequently have UTI. Overall, uncomplicated UTI treatment was mainly initiated by GPs, which corresponds with the Netherlands' policy for UTI to mainly be treated in primary care.

Within the three UTI guideline drugs, proportions of starters with a GP prescription were comparable. Nitrofurantoin remained the mostly preferred UTI antibiotic in starters during the study period and the increase of fosfomycin starters was mainly at the expense of trimethoprim.

Stratification for age categories in 2017 showed that the proportions of women with subsequent antibiotic treatment for febrile UTI increased with age. As this might have been due to treatment failure of the UTI guideline antibiotics, their effectiveness in the elderly should be monitored.

Compared to studies from other countries, the changes in antibiotic preferences in the UTI guideline in the Netherlands quickly corresponded with changes in UTI antibiotic prescriptions. Studies in New Zealand (7) and the US [6, 27] reported poor GP adherence to recommended uncomplicated UTI prescribing guidelines. Percentages of patients treated with fluoroquinolones for uncomplicated UTI varied, from 20% in New Zealand to 50% in the US, and percentages of patients treated with nitrofurantoin varied from 14 to 35%. The quickly implemented changes in the Netherlands may show a high trust of the

GPs in this country to their guidelines and also reflect a good communication in guideline changes and effort for guideline implementation. In the Netherlands, a study on the implementation of Dutch GP guidelines showed that the most preferred implementation strategy by GPs were interactive small group meetings (84% rated this as much or very much encouraging), audit and feedback (53%), organizational interventions like changes in the practice setting (50%) and the use of local opinion leaders (50%) as methods for improving guideline adherence. In the Netherlands, GPs and pharmacists have regular pharmacotherapeutic audit meetings in which guideline changes are discussed [28, 29]. Moreover, in the audit meetings, agreements for improvement are made and subsequently monitored [30]. This complies with the recommendations of a study in the UK to implement a national programme of training and accreditation for medicines optimization pharmacists [9]. Furthermore in the Netherlands, guideline recommendations are implemented in the electronic prescribing systems, which also may have contributed to quick changes in prescribing behaviour [31].

Strengths and limitations

A strength of this study is that dispensing data from a majority of all community pharmacies in the Netherlands were at our disposal. The antibiotics under investigation were available by prescription only; thus, the medication was completely covered by our database.

A limitation of this study is that we did not have information on the diagnoses and the outcome of treatment. On the other hand, the study drugs for uncomplicated UTI are specific for this indication and thus misclassification is unlikely.

Additionally, we were not able to distinguish nitrofurantoin or trimethoprim use for prophylactic use from acute UTI treatment. Continuous antibiotic prophylaxis for 6-12 months reduces the rate of UTI during prophylaxis when compared to placebo. If women with continuous prophylaxis have a recurrence the guideline advises treatment with one of the other guideline antibiotics for uncomplicated UTI. In a period of 12 months, therapeutic use also often overlaps with prophylactic use because (1) continuous antibiotic prophylaxis for 6-12 months reduces the rate of UTI during prophylaxis when compared to placebo, and (2) prophylaxis does not appear to modify the natural history of recurrent UTI and most women revert back to their previous patterns of

recurrent UTI once prophylaxis is stopped [32, 33]. In spite of that, we may have mistaken nitrofurantoin or trimethoprim use for UTI treatment instead of prophylaxis. On the other hand, we do not have any reason to assume that this misclassification would be differential during the years of our study period, and thus we do not expect bias for the comparison of the percentages of drug users during the years. However, should the user numbers of nitrofurantoin and trimethoprim be overestimated, then the estimation of fosfomycin user proportions within all users of UTI treatment might be underestimated.

In our cross-sectional study design, the starters consisted of first-time starters and women that switched from another guideline antibiotic within the same year. On the other hand, we do not expect any bias from comparisons of switching between uncomplicated UTI guideline drugs.

We assumed that a dispensing of ciprofloxacin, amoxicillin/clavulanic acid, or co-trimoxazole within 14 days after an uncomplicated UTI antibiotic indicated progression to febrile UTI, but these antibiotics may have been used for multiple indications. By only including the use of these drugs within a 14-day period after dispensing of one of three uncomplicated UTI guideline antibiotics, we minimised the likelihood that these antibiotics were prescribed for other indications, but this cannot be completely excluded. As ciprofloxacin and amoxicillin/clavulanic acid are used for many different indications, dispensing data did not allow us to analyse the proportion of women with uncomplicated UTI that received these antibiotics as initial medication. Because ciprofloxacin was first choice for treatment of complicated UTI, we expect GPs to prefer this antibiotic, comparable to the treatment for unresponsive UTI, when they chose to prescribe a non-guideline antibiotic for uncomplicated UTI. Moreover, a recent study on the use of antibiotics in the Netherlands compared to Germany showed that overall use of ciprofloxacin in the Netherlands is very limited and much lower than the uncomplicated UTI antibiotics studied [34]. Consequently, while ciprofloxacin and amoxicillin/clavulanic acid may sometimes have been prescribed as initial treatment for uncomplicated UTI, the proportion of women that received these drugs as initial treatment must be negligible.

Summary and Conclusion

This study shows substantial changes in UTI prescribing behaviour after UTI guideline changes in 2013. This may have been facilitated by clear guideline recommendations and a broad implementation strategy with regular pharmacotherapeutic audit meetings and incorporation of the GP guideline recommendations in the electronic prescribing systems.

Acknowledgements

The authors thank Manon Verkroost from SFK and Petra Overbeek from the Laboratorium der Nederlandse Apotheken for their information on dispensings before 2012 and shortages of nitrofurantoin respectively.

3.1

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

None

Ethical standards

The Institutional Review Board of SFK approved this study. Use of observational data in descriptive studies in the Netherlands is not considered to be an interventional trial, according to Directive 2001/20EC of Dutch legislation. Therefore, the study protocol did not need to be submitted to a medical ethics committee for approval.

Author's contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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Supplementary material

Table 1. Numbers of users of two ^j or three ^h different guideline antibiotics for Acute Cystitis, stratified for age categories in 2017

Age category	Number of users ^a of two different guideline antibiotics for acute cystitis ^j (% of all users of two different guideline antibiotics for acute cystitis) N=129,712	Number of users [#] of three different guideline antibiotics for acute cystitis ^h (% of all users of three different guideline antibiotics for acute cystitis) N=11,100
18-20	3,198 (2.5%)	198 (1.8%)
21-30	9,375 (7.2%)	572 (5.2%)
31-40	8,526 (6.6%)	554 (5.0%)
41-50	12,091 (9.3%)	877 (7.9%)
51-60	17,331 (13.4%)	1,318 (11.9%)
61-70	22,945 (17.7%)	1,933 (17.4%)
71-80	26,930 (20.8%)	2,556 (23.0%)
≥81	29,317 (22.6%)	3,091 (27.8%)

^a The number of users was extrapolated to the number of all community pharmacies in the Netherlands in 2017: in 2017 data were available from 1765 community pharmacies (89% of all community pharmacies)

^j nitrofurantoin and fosfomycin/ nitrofurantoin and trimethoprim/ fosfomycin and trimethoprim

^h nitrofurantoin, fosfomycin and trimethoprim

CHAPTER 3.2

Patterns of recurring dispensing of guideline antibiotics for uncomplicated urinary tract infection in women over a 5-year period: Longitudinal patterns of recurring dispensings of Dutch guideline UTI antibiotics

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Family Practice, 2020, 1-6

<http://dx.doi.org/10.1093/fampra/cmaa110>

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Abstract

Background

Urinary tract infection (UTI) is one of the most prevalent medical conditions among women seeking primary care. 20-40% of the women have a UTI recurrence during their lifetime.

Objective

To provide insight in the patterns of recurring annual dispensings for antibiotics commonly used for UTI treatment in women, aged 18 years or older, during a 5-year follow-up period in the Netherlands.

Method

The Dutch Foundation of Pharmaceutical statistics collects dispensing data from more than 90% of all community pharmacies. Pharmacies with complete data between 2011-2017 were included. Women of age 18 years or older with a first dispensing of nitrofurantoin, fosfomycin, or trimethoprim in 2012 and a dispensing of any medication in 2017 were selected. For each year between 2013 and 2017, the proportions of women with recurring dispensing of nitrofurantoin, fosfomycin or trimethoprim were calculated and stratified for age categories.

Results

Within 1,517 eligible community pharmacies, 463,821 women, aged 18 years or older, were dispensed one of the antibiotics in 2012, and 239,292 women still visited the same pharmacy in 2017. About 56% of them received at least one recurring dispensing during five years of follow-up. Each year, approximately 20% of the source population had at least one recurring dispensing. Approximately 2% of the source population had at least one recurring dispensing in each year of follow up.

Conclusion

Over the five-year study period, more than 50% of the source population had at least one recurring dispensing for uncomplicated UTI, most of them with at least one year without UTI dispensing in between.

Background

Urinary tract infection (UTI) is one of the most prevalent medical conditions among women in primary care. Approximately 60% of women experience symptomatic acute cystitis in their lifetime[1]. An estimated 20-40% of women who have had one previous uncomplicated UTI episode are likely to experience recurring UTI[2-4]. Commonly, recurrent UTI is defined as a recurring UTI with a frequency of 3 or more episodes in the last 12 months or 2 or more episodes in the last 6 months [5, 6]. It was shown that the prevalence of UTI (at least one physician-diagnosed UTI per year) increased with age, and in women over 65 years was approximately 20%, compared with approximately 11% in the overall population [7].

Risk factors for recurring UTI can be classified into four categories: (i) factors that decrease normal urogenital flora, e.g. frequent antibiotic use, personal hygiene, spermicide use, diaphragm/pessary use and menopause. (ii) factors that facilitate bacterial entry into the bladder, e.g. sexual intercourse, frequent catheterization and menopause, (iii) factors that decrease bacterial removal, e.g. decreased fluid intake, delayed voiding, incomplete bladder emptying and pelvic organ prolapse and (iv) factors that impair the immune response, e.g. diabetes, steroid use, tobacco use and HIV/AIDS [8]. A US study among women aged 18-49 years showed that UTI histories in first-degree female relatives were a strong and consistent risk factor with an increased risk for each type of relative and higher risk with greater numbers of infections [9]. This study has also showed that the risk in women with combined exposures of a family UTI history and sexual intercourse, frequency was considerably higher than with either exposure category alone.

The burden of recurring UTI has both personal and societal aspects[10-15]. The societal burden includes the clinical and economic burden of illness. The personal burden comprises social and psychological effects which have a negative impact on the quality of life. Costs may be both direct and indirect: work absenteeism, for example, can impact both the economy and a patient's sense of wellbeing [10]. Education about behavioural risk factors is advised for women with recurrent infections [16-19], but this may be relevant also for women with a recurrence of UTI after an interval of one or more years without UTI.

At present no large population-based studies have determined what proportions of women with uncomplicated UTI develop patterns of recurrences. This paper aims to provide insight in patterns of recurring dispensings of guideline antibiotics for treatment of uncomplicated UTI over a 5-year period in community dwelling women.

Methods

An observational descriptive study with routinely collected dispensing data was performed during 5 years of follow up for women, with a first dispensing in 2012 of nitrofurantoin, fosfomycin, or trimethoprim.

Setting

In the Netherlands, the Dutch Foundation of Pharmaceutical statistics (SFK) collects dispensing data from more than 90% of all community pharmacies [20]. The majority of patients visit one community pharmacy, which ensures completeness of the medication record and facilitates clinical risk management [21]. In the SFK database, individuals are registered within a community pharmacy by a unique code generated by the pharmacy software system. By this unique encrypted code, patients can be tracked if they visit the same pharmacy. In the SFK database, information was available on patients' sex and year of birth, by which their age in 2012 could be calculated. Drug dispensings were coded by the Anatomic Therapeutic Chemical (ATC) system [22]. No information on the reason of prescribing (indication) or loss to follow up from the database was available.

Pharmacy inclusion

Community pharmacies were included that had provided complete dispensing data for the period between 1 January 2011 and 31 December 2017 to the SFK.

Patient inclusion

All women, of age 18 years or older, were selected with a first dispensing in 2012 of one of the Dutch GP guideline recommended antibiotics for treatment of uncomplicated UTI. The recommended antibiotics were nitrofurantoin, fosfomycin and trimethoprim. We defined a first dispensing as the absence of a dispensing of an uncomplicated UTI antibiotic during the preceding 12 months, and the presence of an automatically generated code which states that a first

dispensing fee was charged. We included only those women with any medication or medical device in their medication record in the same pharmacy in 2017, as this suggested that a woman was still registered at this pharmacy at the end of the 5-year study period. We reasoned that all dispensings including uncomplicated UTI antibiotics would have been covered for those women throughout the 5 year study period.

Data collection

We retrieved annual information on recurring dispensings of nitrofurantoin, fosfomycin and trimethoprim. Nitrofurantoin and trimethoprim can be used in different dosages and treatment durations, as well as for UTI prophylaxis. The Dutch GP UTI guideline, recommends for uncomplicated UTI treatment, as a first choice nitrofurantoin (ATC [22] code: J01XE01) as a dose of 200 mg/day for 5 days, either 100mg in a controlled release tablet twice daily for 5 days or 50 mg in a regular tablet 4 times daily, as a second choice fosfomycin (J01XX01) as a one-off dose of 3 gram, and as a third choice trimethoprim (J01EA01) as a dose of 300 mg once daily for 3 days.

Data analysis

The number of women with dispensing of nitrofurantoin, fosfomycin and trimethoprim in each year of follow up was divided by the total number of included women with a first dispensing in 2012. The number of women with dispensing in 2012 and in the follow-up years was stratified for age categories.

We used descriptive statistics to analyse the data with SPSS software, version 23 (SPSS Inc., Chicago, IL, USA).

Results

Complete data were available from 1517 community pharmacies (77% of all community pharmacies in the Netherlands in 2012). In 2012, these pharmacies delivered a first dispensing of nitrofurantoin, fosfomycin or trimethoprim to 463,821 women, aged 18 years or older (on an average, 300 women per pharmacy per year). From these women, 239,292 (51.6%) still visited the same pharmacy in 2017 (Table 1) and were taken as the source population. Or the women with a first dispensing of the UTI antibiotics in 2012, 224,529 did not have any dispensing in 2017 within the same pharmacy, and were thus lost to

follow-up, Compared with the source population, the proportions of women lost to follow-up, were higher in the youngest and the oldest age categories, whereas the proportion of women 31-70 years was lower in the lost to follow-up population (Table 1). The mean age of the women in the source population was 54 years (\pm 18.4 years) and ages varied between 18 and 103 years. The median age of women lost to follow up was 47 years and ages varied between 19 and 112 years.

Table 1. Characteristics of included women and of women lost to follow up with a first dispensing of a guideline antibiotic recommended for uncomplicated urinary tract infection in 2012; included women also with at least one recurring dispensing of a guideline antibiotic recommended for uncomplicated urinary tract infection in 2017.

	Women still visiting the same pharmacy at the end of follow up: Source population	Women not visiting the same pharmacy at the end of follow up: Lost to follow up
Number of women \geq 18 years, first prescription [§] of nitrofurantoin, fosfomycin, or trimethoprim in 2012	239,292 (100%)	224,529 (100%)
Numbers of women included/ lost to follow up@ (% of women included/ lost to follow up):		
18-30 years	34,118 (14.3%)	62,523 (27.8%)
31-50 years	69,436 (29.0%)	58,811 (26.2%)
51-70 year	86,117 (36.0%)	45,794 (20.4%)
\geq 71 years	49,621 (20.7%)	57,400 (25.6%)
Numbers of women* with a first prescription in 2012 of (% women included/ lost to follow up):		
nitrofurantoin	202,062 (84.4%)	189,834 (84.5%)
fosfomycin	14,658 (6.1%)	11,535 (5.1%)
trimethoprim	44,248 (18.5%)	38,033 (16.9%)
Numbers of women* with a recurring UTI prescription in 2017 of: (% of all women with prescription in 2017)		
nitrofurantoin	38,796 (74.2%)	
fosfomycin	19,084 (36.5%)	
trimethoprim	3,306 (6.3%)	

§ Data from 1517 community pharmacies (77% of all in the Netherlands in 2012)

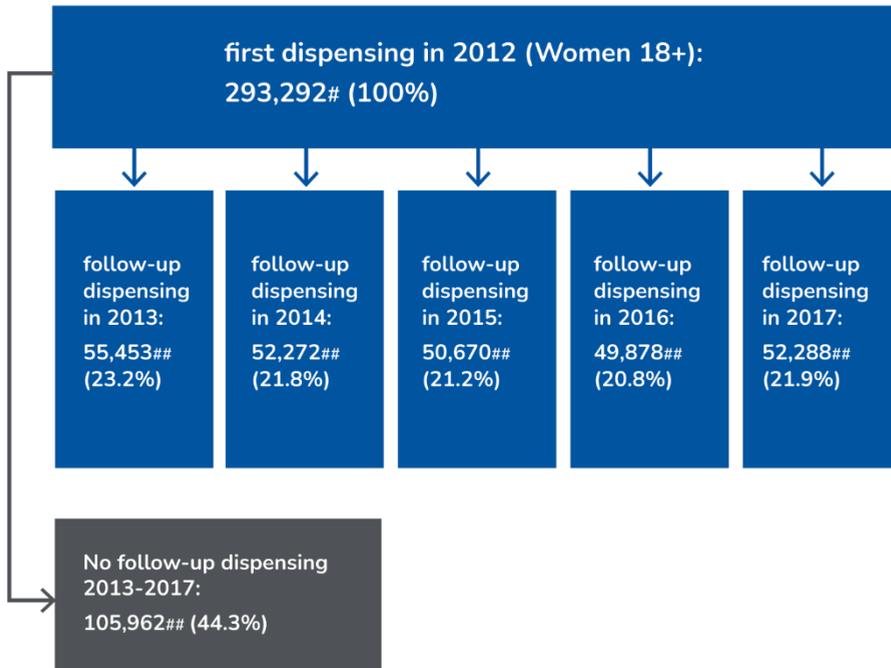
* Numbers of users of uncomplicated UTI antibiotics can add up to more than the women included and proportions up to more than 100%, due to women that had first dispensings of more than one type of antibiotic for uncomplicated urinary tract infection in 2012 and 2017 & women \geq 18 years with a first dispensing in 2012, defined as no dispensing of the same antibiotic drug in the prior 12 month, and a registration for a first dispensing consultation in the pharmacy system with at least one dispensing in the same pharmacy in 2017

@ age categories applied to women's age in 2012

In 2012, 84.4% of the women of the source population received nitrofurantoin, 6.1% of the women received fosfomicin, and 18.5% received trimethoprim. The proportions of women using these antibiotics for those lost to follow-up were comparable to the source population. The proportions of women treated with fosfomicin and trimethoprim in 2017 differed significantly from the proportions of women treated with these antibiotics in 2012. Of the women in the source population, 9.5% ($n = 22,693$) received more than one type of antibiotic in 2012.

From the women of the source population, 55.7% had at least one recurring dispensing of an UTI antibiotic in one of the five years of follow-up. Consequently, 44.3% of those women still visiting the same pharmacy in 2017 did not return for a recurring dispensing of any of these antibiotics during the follow-up period. Figure 1 shows that in each year, from 2013 to 2017, one in five women of the source population returned to the pharmacy for at least one recurring dispensing of nitrofurantoin, fosfomicin or trimethoprim. From the 52,272 women with a recurring dispensing in 2014, 56.6% did not have a dispensing in the preceding year 2013 (data not shown). After 2014, the proportion of women without any dispensing in the preceding years gradually decreased from 39.4% in 2015 to 25.7% in 2017.

Figure 1. Return of women with a first dispensing of a guideline antibiotic for uncomplicated urinary tract infection in 2012[&] to the pharmacy between 2013 and 2017, for at least one recurring dispensing or no recurring dispensing in any year of follow-up.



Women \geq 18 years with a first dispensing in 2012, defined as no dispensing of the same antibiotic in the previous 12 months, and at least one dispensing in the same pharmacy in 2017
 ## Women with at least one dispensing of at least one guideline UTI antibiotic in the corresponding year (proportion of all women included in 2012)

Figure 2 shows for each year of follow-up, the numbers of women with at least one recurring dispensing of nitrofurantoin, fosfomycin or trimethoprim during the corresponding and previous study years. Among these women with recurring dispensing, the proportions of younger women (aged between 19-30 and 31-50 years) were lower than the proportions of older women.

Figure 2. Recurring dispensing during 5 years of follow-up in women with a first dispensing of a guideline antibiotic for uncomplicated urinary tract infection in 2012[&]

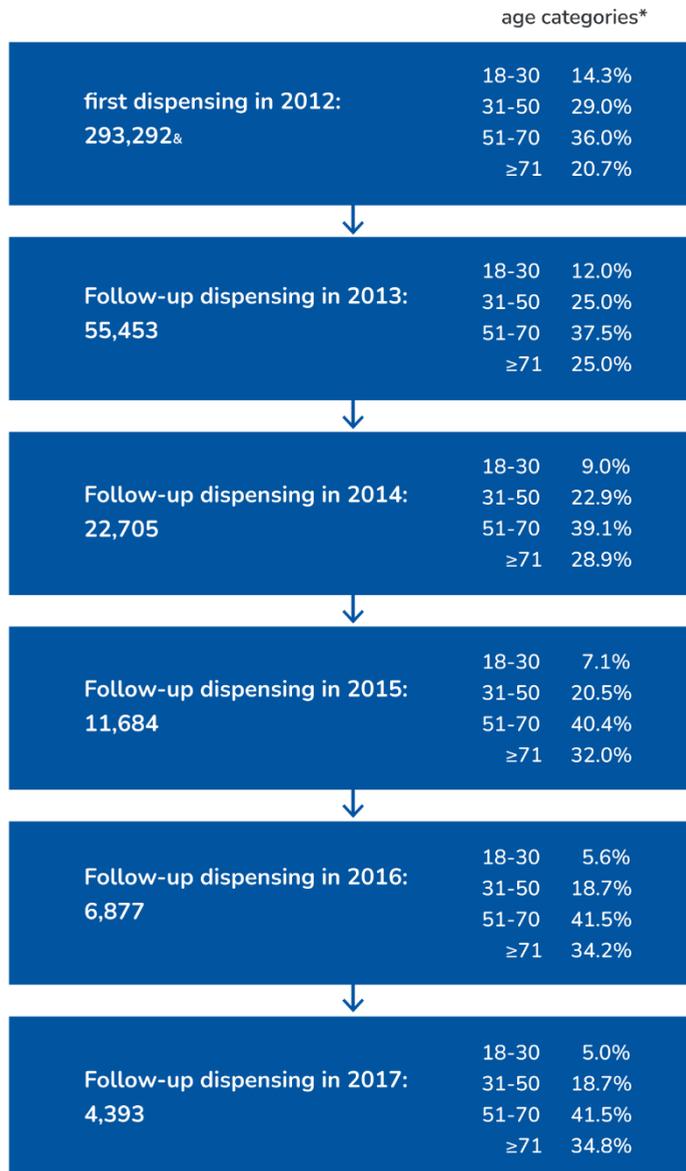


Table 2 shows that the proportion of women without any recurring dispensing during follow up was highest in the youngest age group (50.5%) and lowest in the oldest age group (36.6%). From the women of the source population, 25.7% ($n = 61,517$) had at least one recurring dispensing in a year of follow-up, whereas 1.8% ($n = 4393$) had at least one recurring dispensing in each year of follow up.

Table 2. Number of women with a first dispensing for uncomplicated urinary tract infection in 2012 [§] with total number of years of follow up, every year with at least one recurring dispensing, stratified for age categories

Age	18-30	31-50	51-70	≥71	Sum
No recurring dispensing during follow up (% within age category)	17,240 (50.5%)	33,872 (48.8%)	36,672 (42.6%)	18,178 (36.6%)	105,962 (44.3%)
Recurring dispensing during 1 year of follow up	9,429 (27.6%)	17,981 (25.9%)	21,648 (25.1%)	12,459 (25.1%)	61,517 (25.7%)
Recurring dispensings during 2 years of follow up	4,548 (13.3%)	9,614 (13.8%)	13,438 (15.6%)	8,389 (16.9%)	35,989 (15.0%)
Recurring dispensings during 3 years of follow up	1,944 (5.7%)	4,889 (7.0%)	8,094 (9.4%)	5,696 (11.5%)	20,623 (8.6%)
Recurring dispensings during 4 years of follow up	738 (2.2%)	2,260 (3.3%)	4,441 (5.1%)	3,369 (6.8%)	10,808 (4.5%)
Recurring dispensings during 5 years of follow up	219 (0.6%)	820 (1.2%)	1,824 (2.1%)	1,530 (3.1%)	4,393 (1.8%)
Sum of all women	34,118 (100%)	69,436 (100%)	86,117 (100%)	49,621 (100%)	239,292 (100%)

§ Data from 1517 community pharmacies (77% of all community pharmacies in the Netherlands in 2012)

& women ≥18 years with a first dispensing in 2012, defined as no dispensing of the same antibiotic in the prior 12 months, and at least one dispensing in the same pharmacy in 2017

@ age categories applied to women's age in 2012

Discussion

Our results show that more than half of the women still visiting the same pharmacy at the end of the study period had at least one recurring dispensing of a guideline antibiotic for uncomplicated UTI during five years of follow-up. Within a subsequent year, the proportions of another UTI dispensing were between 20% and 23%. This proportion is within the range of 20-40% that was reported earlier for recurrent UTI [2, 4]. A Finnish study among women aged 17–82 years reported 44% UTI recurrence within 1 year [23]. In these studies, recurrent UTIs were defined as three or more episodes in 12 months. Our definition of recurring UTIs was less strict, counting at least one recurring prescription of an UTI antibiotic.

About 2% of the women included in our study received at least one recurring dispensing during every year of 5 years of follow up. Most of these women belonged to the age category 51–70 years. In this age category most women are menopausal, and menopause was reported as one of the risk factors for UTI [8].

As UTI is one of the most prevalent medical conditions among women in primary care and approximately 60% of women experience symptomatic acute cystitis in their lifetime [1], UTI provides a high workload for primary care. In recent years, there have been increasing concerns in several countries about the rising workload in general practice, amongst others caused by the increase of multi-morbidity and chronic diseases, an aging population, and the pressure to reduce access to secondary care [24]. Moreover, the increasing costs of the healthcare system demand changes in the organisation of care [25].

Stimulating patients' self-management to prevent recurring episodes of uncomplicated UTI seems to be a logical approach. There is of course always concern on overuse of antibiotics resulting in increasing antimicrobial resistance [26].

Women with recurring UTI may need additional care to improve selfmanagement, aimed at prevention of uncomplicated UTI in the future. The GP or another healthcare provider can provide this additional care for women with recurring UTI [27, 28]. However, it may be preferable to educate women on preventive actions or discuss with them delay of antibiotic treatment with increased fluid intake and painkillers [29], before starting patient-initiated

treatment [30]. A study showed that UTI symptoms recovered spontaneously within one week in about 50% of symptomatic women not taking antibiotics [31]. Other studies showed that more than one third of women with UTI symptoms were willing to delay antibiotic treatment when asked by their GP [32]. Women preferred not to take antibiotics and were open to alternative management approaches [33].

This study provides insight in the patterns of recurring dispensings for guideline antibiotics for uncomplicated UTI and an indication of the size of the problem. Further work needs to be done to identify predictors of recurring prescribing and to study the effect of education about risk factors on recurring prescribing.

Strengths and limitation

A strength of our study was that we used routinely collected dispensing data from a majority of community pharmacies in the Netherlands, which enabled us to follow nearly 250,000 female users of guideline recommended antibiotics for uncomplicated UTI for 5 years. In the Netherlands all antibiotics for UTI treatment are only available through prescription and 90% of patients visit the same pharmacy [21]. Because of this the medication was almost completely covered by the database.

Another strength is that, although we lacked the reason for prescribing, uncomplicated UTI is the only indication for nitrofurantoin, fosfomycin, and trimethoprim in the electronic GP prescription module. On the other hand, nitrofurantoin and trimethoprim may also be used for UTI prophylaxis at different dosages and durations of use. In our study, only dispensings for women with a guideline recommended dosage and duration were counted as recurring dispensings. By doing so, we also excluded slightly different dosage regimens for pregnant women and other risk groups (for example diabetes comorbidity).

A limitation in our study was that women were coded within the community pharmacies and could not be followed for dispensings from another pharmacy. Therefore we included only those women that still had any dispensing within the same pharmacy at follow-up after 5 years. This, however, led to the exclusion of almost half of all women with a first dispensing in 2012. The youngest and oldest age groups were relatively more present in those women that could not be followed until the end of the study (Table 1). This may be

due to moving or death. Statline, the National Statistics Database in the Netherlands provided yearly data on the proportions of people moving within municipalities and entering other municipalities per 1000 inhabitants, and the relative number of deceased [34]. From these data, 43% of the population moved within a municipality or into another municipality or died between 2012 and 2017. This proportion is comparable to the 48% lost to follow-up in our study. Therefore, we conclude that the loss of follow up is not related to our research question and thus is not likely to create bias to our results on the prevalence of recurring UTI dispensings in women.

Another limitation was that we did not analyse what proportion of the source population had recurrent UTI. We did not do this because our aim was to analyse recurrence of UTI in all women over a 5 year period.

We also may have missed some recurring dispensings in women who incidentally visited another pharmacy for out-of-hours services. This would lead to underestimation of the proportion of women with recurring dispensings.

Conclusion

This study shows that over the 5-year study period, more than 50% of the women had at least one recurring antibiotic dispensing to treat uncomplicated UTI. Patient empowerment is needed to prevent recurrence of UTI and antibiotic treatment, and healthcare providers can play an important role in this. They can discuss risk factors for UTI with women and educate them on preventive actions. Also, GPs can discuss with women delay of antibiotic treatment with increased fluid intake and painkillers.

Ethical approval

The independent advisory board of SFK approved the use of their anonymised and encrypted data for this study. Use of anonymous observational data in the Netherlands is not considered as subject to ethical approval from an independent medical ethical committee.

Funding

No sources of funding were used to assist in the conduct of this study or the preparation of this article.

Conflict of interest

The authors declare that they have no competing interests.

Author's contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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CHAPTER 3.3

Womens' self-management skills for prevention and treatment of recurring urinary tract infection

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Int J Clin Pract. 2021;75:e14289.

<https://doi.org/10.1111/ijcp.14289>

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Abstract

Background

The guideline on urinary tract infections (UTI) of the Dutch College of General Practitioners provides recommendations on patient-initiated treatment and prevention of recurring UTI.

Aim

To study familiarity with self-management skills for prevention of recurring UTI amongst adult women.

Design and setting

An online questionnaire was developed, based on the UTI guideline and interviews with women having recurring UTI. Pharmacists in a postgraduate education programme ($n = 76$) aimed to invite ten adult women with a recurring UTI prescription to complete the questionnaire. Women were asked for informed consent to link medication record data to questionnaire data.

Method

We calculated proportions of the scores for self-management skills and analysed differences between age groups with chi-square test.

Results

Complete questionnaires were available for 719 women (mean age 55.1 ± 18.5 years). The proportions of women 18-50 years and women 51 years or older were 36.4% and 63.6%, respectively. Education levels of women 18-50 years were significantly higher than those of women 51 years and older. Before consulting a general practitioner (GP) for symptoms, 32.1% of all women increased fluid intake; additionally, 15.0% used analgesics and increased fluid intake. Of all women, 33.9% searched internet for information on self-management and 18% occasionally received a prescription for patient-initiated treatment, half of these for use during vacation. Cranberry was used by 47%, d-mannose by 5%, and vitamin C by 29% of all women. Awareness of different preventive behavioural actions (e.g. fluid intake, washing without soap, emptying bladder after sexual intercourse) varied between 20% and 90%.

Conclusion

Almost half of all women applied self-management (increased fluid intake, analgesics) before consulting a GP for recurring UTI. Awareness of preventive behavioural actions for recurring UTI varied considerably. Thus, education of women about the use of analgesics and behavioural actions deserves attention.

Introduction

Uncomplicated urinary tract infections (UTI) are amongst the most common acute presentations for women in primary care [1]. During their lifetime, 40% to 60% of women are at least once diagnosed and treated for a UTI, with most being diagnosed for the first time before the age of 25 [2, 3]. Approximately one third of women experience at least one recurring UTI, often within 3 months after the first episode [4]. In 2017, UTI was the most frequent indication for a general practitioners' (GP) prescription of an antibiotic in the Netherlands [5].

In most women, UTIs are accompanied by symptoms such as dysuria, urgency, frequent urination, suprapubic pain and hematuria [6]. In post-menopausal women, however, genitourinary symptoms are not necessarily related to uncomplicated UTI [7]. The diagnosis of uncomplicated UTI can be made with a high probability based on a history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge [7, 8]. In 25% to 50% of symptomatic women not taking antibiotics, symptoms recover spontaneously within one week [9]. More than a third of women with UTI symptoms were willing to delay antibiotic treatment when asked by their GP [9]. In addition, women themselves may prevent recurrence of UTI.

Recent studies have identified several risk factors for recurring UTI: wiping back to front; delayed or premature voiding; straining to void; not voiding urine within 15 min after intercourse; using soap to clean after urination; and chronic constipation [10-13]. The 2013 Dutch GP guideline recommends ample fluid intake, complete emptying of the bladder, not postponing micturition, emptying of the bladder soon after intercourse, and prophylactic use of cranberry [14, 15]. A Cochrane review concluded that there is limited evidence for the benefit of cranberry for preventing recurring UTI [16]. In 2019, the GP guideline was revised. Prophylactic use of cranberry and d-mannose were mentioned as potential preventive actions, in spite of limited evidence [17, 18]. Vitamin C has been recommended in the past. Its use was thought to inhibit bacterial growth by acidifying the urine. However, there is inconclusive evidence for the effectiveness of Vitamin C in prevention [19, 20].

Prevention strategies other than antibiotic prophylaxis carry a low risk of adverse effects, do not increase bacterial resistance and should be considered

in order to minimise use of antibiotics [6, 7, 21-23]. Therefore, it is important to know what women already know and do to prevent recurring UTI. However, studies of the perceptions of women on the prevention of recurring UTI are limited.

We studied self-management skills and knowledge of behavioural actions aimed at preventing recurring UTI in adult women (aged 18 years and older).

Method

Study design

Women were invited for an online survey in 76 Dutch community pharmacies spread across the Netherlands. The pharmacists who participated in the study were enrolled in a postgraduate education programme to specialise in community pharmacy. They invited ten adult women who visited the pharmacy with a prescription of one of the UTI guideline antibiotics (nitrofurantoin, fosfomycin, or trimethoprim) for treatment of uncomplicated UTI. Women who were not proficient in Dutch or never before had UTI were excluded. Moreover, included women were asked for permission to consult their medication record of the preceding 12 months for the number of dispensings of UTI antibiotics. Patients were asked for informed consent regarding the use of the anonymised data in the questionnaire and medication record. For identification of these documents, they received a four-digit research code. The pharmacists kept a secure coding table with the four-digit code and patient identification data in the pharmacy. The researchers had no access to data that could identify individual patients. The researchers communicated with the postgraduate trainees through the coordinator of the curriculum, who acted as a 'trusted third person'. After one month, the pharmacists sent a reminder to patients who had not yet responded. Data were collected between March and July 2018.

Data collection

The survey was conducted using an online survey system (Questback Version 27). The women could complete the questionnaire online in this survey tool or via a paper form in the pharmacy. The pharmacists entered data from the paper form into the survey tool. Medication record printouts were screened for the number of dispensings of nitrofurantoin 200mg for five or seven days,

fosfomycin as a one-off dose of 3 gram, and trimethoprim 300mg for three days.

Questionnaire design

The questionnaire was designed after semi-structured, face-to-face interviews with three adult women who had recurring UTI. The interviews were digitally recorded, transcribed verbatim, and analysed. Questions were based on these interviews and the recommendations of the 2013 version of the UTI guideline of the Dutch College of General Practitioners [14]. The questionnaire was piloted for clarity, presentation, and missing items by two women reading the questionnaire aloud. Main topics in the questionnaire were patient-initiated treatment and self-management strategies. Answers were multiple-choice, open response, and a five-point Likert scale, ranging from totally disagree to totally agree.

Data analysis

Descriptive analyses (proportions and means) were calculated. For Likert-scale questions, a positive or negative answer was calculated by adding (dis)agree and totally (dis)agree. Considering that symptoms may change with menopause and that differences in education levels may exist, we stratified the results for women 18-50 years and for women 51 years and older. Chi-square tests and independent sample t-tests were used to assess statistically significant differences in patient characteristics and outcome between the two age groups. All data were analysed using IBM SPSS for Windows, version 23.0.

Results

Response rate and population

Seven hundred forty-three women completed the questionnaire. Of these, 24 were excluded for missing of the four-digit research code or age. Therefore, the study population consisted of 719 women (Table 1). The proportions of women 18-50 years and women 51 years or older were 36.4% and 63.6%, respectively. Education levels of women 18-50 years were significantly higher than those of women 51 years and older.

The analysis for the number of dispensings in the medication record could be performed on a subgroup of 545 women who gave informed consent to

consult their medication record and provided a complete medication record of 12 months. Of these women, 49.9% (n = 277) had one or two dispensings in the preceding year. Women 18-50 years had significantly less dispensings than women 51 years and older.

Table 1. Characteristics of participating women with recurring urinary tract infection, stratified for age groups

	All women	Women 18-50 years	Women ≥ 51 years	p-value
All questionnaires				
Number of women	719 (100%)	262 (100%)	457 (100%)	
Mean age (± sd) in years	55.1 ± 18.5	34.2 ± 9.8	67.1 ± 9.5	
Education		*	*	<i>P</i> < 0.001
Primary	35.9% (258)	16.0% (42)	48.3% (216)	
Secondary	36.2% (260)	44.3% (116)	32.2% (144)	
Higher	28.0% (201)	39.7% (104)	21.7% (97)	
Questionnaires of women with medication records				
Number of women	545	194 (35.6%)	351 (64.4%)	
Mean number of self-reported episodes in the preceding 12 months ±sd (range)	3.1 ± 1.4 (0-15)	3.1 ± 1.3 (1-10)	3.2 ± 1.4 (1-15)	
Mean number of dispensing of uncomplicated UTI antibiotics in the preceding 12 months ±sd (range)	3.0 ± 1.9 (0-15)	2.6 ± 1.6 ** (0-10)	3.2 ± 2.1 ** (0-15)	<i>P</i> < 0.001

* statistical significance tested by chi-square test, difference significant if $p < 0.05$

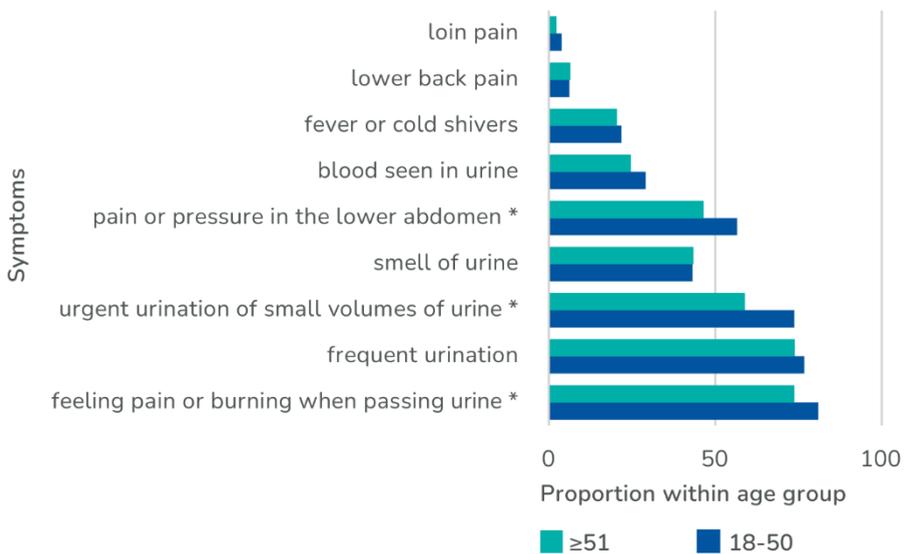
** statistical significance tested by Independent-samples t-test, difference significant if $p < 0.05$

Symptoms

The most common symptoms were dysuria, frequent urination, and urgency (Figure 1, Appendix 1). Recognition of an episode of UTI, based on the symptoms, was reported by 92.9% (n = 668) of all women. Of these women, 48.5% (n = 324) reported a combination of dysuria, frequent urination, and

urgency. This combination of symptoms and association with recognition of UTI was significantly more present within women 18-50 years (56.7%) than within older women (43.7%) ($p = 0.001$). Of all women, 87.6% ($n = 630$) thought an antibiotic was always necessary when they experienced an episode: 90.6% ($n = 414$) of women 51 years and older, and significantly less in women 18-50 years, with 82.4% ($n = 216$) ($p = 0.001$). Of the women with a medication record, 42.2% ($n = 234$) recognised an episode of UTI based on the three symptoms. Of these women, 42.7% ($n = 113$) had one or two dispensings in the preceding year.

Figure 1. Proportions of women within age groups 18-50 years and 51 years and older for self-reported symptoms; * statistical significance tested by chi-square test to compare proportions of women within age groups, difference significant if $p < 0.05$



Self-management

Upon first symptoms of UTI, 45.2% ($n = 325$) of the study population consulted a GP, whereas 32.1% ($n = 213$) first increased fluid intake before visiting a GP, 15.0% ($n = 108$) first increased fluid intake and used analgesics, and 3.3% ($n = 24$) first increased fluid intake and used cranberry, vitamin C, or d-mannose before consulting a GP. Only 17.8% ($n = 128$) of the study population received a prescription for self-initiated antibiotic treatment. Of these women, 52.3% ($n = 67$) received this prescription on request before

going on holiday. Table 2 shows reported preventive actions and use of nonprescription drugs. Complete bladder emptying was reported by 67.6% (n = 486) of all women, of whom 42.2% were familiar with one of four complementary options (urinating for a long time, relaxation of the bladder, sitting up straight with feet on the ground, tilting the pelvis when urinating stops).

Table 2. Preventive actions taken by adult women to prevent recurring UTI

	All women n = 719	18-50 years n = 262	≥51 years n = 457	p-value
Behavioural actions				
Ample fluid intake	88.0% (633)	89.7% (235)	87.1% (398)	
Complete emptying of the bladder	67.6% (486)	65.6% (172)	68.7% (314)	
Urinating for a long time	33.9% (248)	34.7% (91)	33.9% (155)	
Relaxation of the bladder	22.3% (163)	26.7% (70)	19.9% (91)	
Sitting up straight, feet on the ground	33.5% (245)	31.7% (83)	34.8% (159)	
Tilting the pelvis when urinating stops	26.3% (192)	26.7% (70)	25.6% (117)	
Not postponing micturition	64.4% (463)	65.6% (172)	63.7% (291)	
Emptying bladder soon after sexual intercourse	45.9% (330)	74.4% (195)*	29.5% (135)*	< 0.001
Washing without (alkaline) soap	53.7% (386)	55.3% (145)	52.7% (241)	
Wiping buttocks from front to back	61.9% (445)	65.6% (172)	59.7% (273)	
Nonprescription drugs				
Cranberry capsules	33.9% (244)	29.8% (78)*	36.1% (165)*	< 0.05
Cranberry drink	18.1% (130)	18.7% (49)	17.7% (81)	
D-mannose	4.6% (33)	5.0% (13)	4.4% (20)	
Vitamin C	29.1% (209)	28.6% (75)	29.3% (134)	

Note: Abbreviation: UTI, urinary tract infections

* statistical significance tested by chi-Square test, difference significant if $p < 0.05$

Source of information

Of all women, 39.9% (n = 287) searched the internet for information on self-management of UTI, whereas 8.8% (n = 63) looked for information in magazines. The proportion of women seeking information on the internet was significantly higher for the younger group of women, 18-51 years, with 57.3% compared to 30.0% in older women ($p < 0.001$). However, proportions for looking up information in magazines were significantly higher for women 51 years and older, with 10.9% compared to 5.0% in younger women ($p < 0.05$). Friends and family provided information to 28.8% (n = 207) of the women, a GP to 55.9% (n = 402), a pharmacist to 23.8% (n = 171), and a medical specialist to 5.4% (n = 39).

Discussion

Summary

Half of all women applied self-management for an episode of recurring UTI before consulting a GP. Awareness of different preventive behavioural actions for recurring UTI varied between 20 and 90%.

Strengths and limitations

A strength of this study is that we obtained a large number of questionnaires and medication records from women 18 years and older. Another strength is that the survey was anonymous, which may have stimulated women to give candid answers. Most women filled in the questionnaire online. By providing a choice between filling in the questionnaire online or completing it on paper in the pharmacy, women with limited digital skills could also be included. Nonetheless, women who were not proficient in Dutch were excluded.

However, it is still possible that women with a low literacy level refused to cooperate when asked. Since we only asked for education levels in the questionnaire, we have no record of literacy levels of women who refused to cooperate. Thus, our study may be less representative of this group. On the other hand, this effect may be limited for the older age group as primary, secondary and higher education levels in this group were comparable to national data for women 55 years and older in 2018 with 52%, 30% and 18% respectively [24]. Primary, secondary and higher education levels for the younger age group with 36%, 36% and 28% respectively, differed from the

national levels for women 15-55 years with 25%, 34% and 40% respectively. Thus, the overall education level of the age group 18-50 years was lower than the overall national education level. Since most of the results of the younger and older age groups were comparable, this difference does not seem to have influenced the results.

According to the 2013 GP guideline, we asked women about ample fluid intake. A limitation is that we did not ask about the precise quantity of fluid intake.

Comparison with existing literature

The use of analgesics was mentioned by 15% of women. This proportion is higher than reported in an earlier study in GP practices which found that, in the Netherlands, despite GP guideline recommendations, analgesic prescriptions or advice to buy analgesics without prescription were negligible [25]. This study only analysed the use of analgesics prescribed or advised by a GP in a consultation, whereas we asked women whether they used an analgesic before consulting a GP.

Emptying the bladder soon after sexual intercourse seems better known to younger women, which may be the result of less sexual intercourse in older women. On the other hand, as with younger women, a study showed that recent sexual intercourse is strongly associated with incidental UTI in generally healthy post-menopausal women [26]. Thus, our finding may also be caused by less knowledge of older women who consulted the internet less frequently or by a lack of articles about sexual topics in magazines.

Cranberry was used by almost 50% of the study population, which seems relatively high, considering the limited evidence, but data on the extent of use have not been previously reported. Almost 20% of women reported the use of cranberry juice. As the acceptability of the taste of pure cranberry juice is low, it is likely that most women use cranberry beverages with a limited amount of cranberry [16]. D-mannose was self-reported by a very low proportion of women and was not mentioned in the 2013 GP guideline. However, nowadays d-mannose is mentioned in the revised UTI guideline [15], which might increase the use of d-mannose in coming years. Vitamin C was used by almost one third of women. This proportion seems rather high, considering the limited

evidence for the effectiveness of vitamin C and the risk of urolithiasis in doses of 500-2000 mg per day [27].

Implications for Research and/or practice

Considering that three-quarters of women felt pain or burning when passing urine, women should be actively questioned about their actions taken before consulting a GP and informed about the use of analgesics. This intervention might increase their willingness to apply self-management.

Over 90% of women recognised a recurring UTI episode, whereas almost 50% of them recognised it based on the three primary symptoms. Of the women with a medication record that recognised UTI based on these three symptoms, approximately 50% had one or two episodes in the preceding 12 months. This finding also shows that even women with a limited number of episodes may be able to recognise a UTI episode.

The proportion of women that reported a prescription for self-initiated treatment in previous years was 18%, and almost half of them received it for as needed use during a holiday. Considering that almost 50% of women recognised an episode of UTI based on three symptoms, they might qualify for self-initiated treatment [28], provided they use it appropriately and recognise differential and alarm symptoms. This possibility should be discussed with women who are eligible for self-initiated treatment.

Of the behavioural preventive actions, ample fluid intake was reported most frequently; nevertheless, only 50% reported increasing fluid intake before consulting a GP. Moreover, since 'ample' is subject to personal interpretation, fluid intake should be quantified. Women with recurring UTI can be advised to drink more fluids with individualized volume based on a patient's specific circumstance [29, 30]. The revised 2019 GP guideline recommends an increase of fluid intake up to three litres per day, accounting for comorbidities such as heart failure [15].

Over 60% of women reported complete emptying of the bladder. However, when questioned about how this emptying was achieved, 40% of these women were familiar with only one of four complementary options (urinating for a long time, relaxation of the bladder, sitting up straight with feet on the ground, tilting the pelvis when urinating stops). The other behavioural actions (no postponing of micturition, washing without soap, emptying bladder soon

after sexual intercourse and wiping front to back) were self-reported by 45% - 70% of women. These results show ample room for improvement and should be discussed in consultations with women [31].

The Dutch 2019 GP guideline recommends evaluating the use of cranberry or d-mannose after several months but within the span of one year [15]. However, as these are nonprescription drugs, healthcare providers should question women actively about use, not only of cranberry and d-mannose, but also of vitamin C.

More than 50% of women aged 18-50 years found information on the internet. As this proportion will probably increase in forthcoming years, it is crucial for healthcare providers to discuss with women their information sources and to recommend reliable sources of information. Healthcare providers should discuss with women with recurring UTI practical ways to prevent and self-manage an episode, advising them on how to improve outcomes that decrease the number of antibiotics prescribed for recurring UTI.

Conclusion

This study shows that almost 50% of women already used some form of self-management before consulting a GP. The majority of women had limited awareness of the risk factors and self-administered prevention of UTI. Hence, healthcare providers should pay more attention to educating women with recurring UTI about non-antibiotic prevention.

Acknowledgements

The authors thank the young pharmacist groups in the postgraduate workplace-based curriculum and Caroline van de Steeg PhD, coordinator of the EPA, 'Initiating, performing and/or taking part in practical research'.

Funding

No funding sources assisted in the conduct of this study or the preparation of this article.

Conflict of interest

The authors have no competing interests.

Ethical approval

This study was submitted to the Medical Ethical Review Board of Utrecht Academic Hospital, which confirmed that no ethical approval was required as the study was not subject to the Medical Research Involving Human Subjects Act (WMO).

Author's contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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Supplementary material

Table 1. Proportions of women within age groups 18-50 years and 51 years and older for self-reported symptoms

Symptoms	All women	18-50 years	≥51 years
feeling pain or burning when passing urine	76.2% (548)	80.9% (212)*	73.7% (336)*
frequent urination	74.8% (538)	76.7% (201)	73.9% (337)
urgent urination of small volumes of urine	64.1% (463)	73.7% (193)*	58.8% (268)*
smell of urine	43.3% (311)	43.1% (113)	43.4% (198)
pain or pressure in the lower abdomen	50.1% (360)	56.5% (148)*	46.5% (212)*
blood seen in urine	26.1% (188)	29.0% (76)	24.6% (112)
fever or cold shivers	20.9% (150)	21.8% (57)	20.4% (93)
lower back pain	6.3% (45)	6.1% (16)	6.4% (29)
loin pain	2.8% (20)	3.8% (10)	2.0% (10)

*statistical significance tested by comparing numbers within age groups with chi-square test, difference significant if $p < 0.05$

Table 2: Questionnaire Adult Women With Recurring Urinary Tract Infection (UTI)

1 Please fill in the 4-digit code you received from the pharmacist	
2 How many episodes of uncomplicated UTI have you had (including the present one) in the preceding 12 months	
3 What complaint(s) do you experience in episodes of uncomplicated UTI?	
Pain or burning when passing urine	76.0% (422)
Frequent urination	74.6% (414)
Urgent urination of small volumes of urine (droplets)	63.4% (352)
Unusual smelling urine	43.1% (239)
Pain or uncomfortable pressure in the lower abdomen	50.8% (282)
Blood seen in urine	27.2% (151)
High body temperature (chills, fever)	22.0% (122)
Loin (low back) pain	9.7% (54)
4 Are you able to recognise an episode of uncomplicated urinary tract infection?	
Yes	92.6% (514)
No	2.9% (16)
Sometimes	3.4% (19)
5 When you have complaints of uncomplicated UTI, what action do you take?	
I consult the GP as soon as possible	45.4% (252)
I drink more and consult the GP if that does not diminish my complaints	32.6% (181)
I drink more and use painkillers, and consult the GP if that does not diminish my complaints	14.6% (81)
Other; I self-initiate treatment with the course of antibiotics I have at home, or which I collect from the pharmacy	1.3% (7)
Other; I wait for a number of days	2.9% (16)
Other; I drink more, use cranberry, vitamin C or d-mannose, and consult the GP if that does not diminish my complaints	1.3% (7)
Other; I consult the medical specialist	2.2% (12)
6 When you have an episode of uncomplicated UTI, do you always need a course of antibiotics?	
Yes	87.4% (485)
No	11.7% (65)
7 When you have an episode of uncomplicated UTI or want to prevent one, what do you do yourself?	

Drink plenty of fluids	88.1% (480)
Avoid postponing micturition	64.0% (355)
Empty my bladder soon after sexual intercourse	42.5% (236)
Completely empty the bladder	66.5% (369)
Wash without (alkaline) soap	52.3% (290)
Wipe buttocks from front to back	59.3% (329)
Use cranberry capsules	32.1% (178)
Use cranberry drink	16.9% (94)
Use d-mannose	4.7% (26)
Use vitamin C	28.6% (159)
Other; Shower before sex, urinate standing up, use ibuprofen, eat fruit, drink lemon or orange juice, agrimony or goldenrod tea, have apple vinegar	6.7% (37)

8 | When you completely empty your bladder, how do you do this?

Urinate for a long time	52.2% (191)
Relax the bladder	35.0% (128)
Sit up straight, feet on the ground	48.1% (176)
Strain when urinating	19.4% (71)
Tilt the pelvis when urinating stops	39.6% (145)
Urinate standing up	1.4% (5)
Other; Not specified	2.5% (9)

9 | If you use cranberry, when do you use it?

Only when I have an episode of uncomplicated UTI	38.9% (216)
Every day to prevent an episode of uncomplicated UTI	35.1% (195)

10 | If you use d-mannose, when do you use it?

Only when I have complaints of an episode of uncomplicated UTI	1.1% (6)
Every day to prevent an episode of uncomplicated UTI	3.4% (19)

11 | If you use vitamin C, when do you use it?

Only when I have complaints of an episode of uncomplicated UTI	9.2% (51)
Every day to prevent an episode of uncomplicated UTI	19.3% (107)

12 | Where do you find information about what steps you can take yourself?

Internet	39.3% (218)
Magazines	8.8% (49)
Family and friends	29.0% (161)

GP	56.6% (314)
Pharmacy	23.6% (131)
Medical specialist	5.4% (30)
Other; Own experience, home care, working in healthcare, physiotherapist	11.0% (61)

13 | For complaints of uncomplicated UTI, I can consult my GP at short notice:

totally agree	53.3% (296)
agree	34.4% (191)
neutral	6.3% (35)
not agree	4.0% (22)
totally not agree	1.4% (8)

14 | When you have complaints of uncomplicated UTI, do you have to hand in urine for a diagnostic test?

Yes, only for the first episode of uncomplicated urinary tract infection	10.3% (57)
Yes, only if the complaints have not decreased or disappeared after a course of antibiotics	5.6% (31)
Yes, always	81.6% (453)
Yes, before and after the course of antibiotics	0.5% (3)
No	3.2% (18)
Other; Sometimes	2.5% (14)

15 | When I have an episode of uncomplicated UTI, I can start a course of antibiotics at short notice:

totally agree	47.0% (261)
agree	33.3% (185)
neutral	8.6% (48)
not agree	8.3% (46)
totally not agree	2.5% (14)

16 | Have you ever been given a prescription for a course of antibiotics to be used in the event of a future episode of uncomplicated UTI?

Yes	17.8% (99)
No	78.4% (435)
Other; I don't know	2.9% (16)

18 | If you ever have had a prescription for treatment of a future episode, what was it intended for?

For a holiday (when I asked for it)	9.0% (50)
To pick up at the pharmacy in case of complaints of an episode of uncomplicated urinary tract infection	1.6% (9)

To always have an antibiotic course at hand	7.0% (39)
19 Have you ever had a prescription for prevention of an episode of uncomplicated UTI?	
No	83.6% (464)
Yes, 1 tablet per day	10.5% (58)
Yes, 1 tablet to take after sexual intercourse	2.7% (15)
Yes, cream or ovules (a suppository for use in the vagina) with hormones taken once a day	2.0% (11)
Other; Fosfomycin once every 5, 7 or 10 days	0.9% (5)
20 Do you always visit the same pharmacy?	
Yes, always	460 (82.9%)
Yes, usually	80 (14.4%)
No	2.5% (14)
21 Would you like to consult the pharmacist for a course of antibiotics for an episode of uncomplicated UTI without consultation with your GP?	
Yes, in the consulting room of the pharmacy	9.0% (50)
Yes, provided that the pharmacy validates the episode with a diagnostic test	26.5% (147)
Yes, provided that I can validate the episode with a diagnostic test at home	18.4% (102)
Yes, at the pharmacy counter	17.7% (98)
No	20.0% (111)
Other, not specified	8.1% (45)
22 I am content with the opening hours of the pharmacy:	
totally agree	45.4% (252)
agree	40.5% (225)
neutral	7.9% (44)
not agree	4.9% (27)
totally not agree	0.7% (4)
23 What is your age?	
24 What is the highest level of education you have completed?	
Primary education	36.2% (201)
Secondary education	36.2% (201)
Higher education	26.3% (146)

CHAPTER 4

Potential role of the community pharmacist in prevention and treatment of recurring acute urinary tract infection

Photo: Visualisation of minimum daily fluid intake (1.5 liter) for prevention of acute cystitis



CHAPTER 4.1

Survey on general practitioners' and pharmacists' opinions regarding patient-initiated treatment of recurring urinary tract infections

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International Journal of Clinical Pharmacy

<https://doi.org/10.1007/s11096-021-01295-2>

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Abstract

Background

The Dutch general practitioners (GP) guideline for urinary tract infections (UTI) recommends patient-initiated treatment for women with recurring UTI. In countries other than the Netherlands, community pharmacists play a role in dispensing antibiotics for recurring UTI without preceding GP consultation.

Objective

To study GP and pharmacist opinions regarding patient-initiated treatment, including pharmacist support for, and consequences of, facilitated access to antibiotics.

Setting

Dutch community pharmacies that cooperate with at least two GPs in their regional primary care network.

Method

Pharmacists in a postgraduate education program invited their residency pharmacist and 2–3 GPs to anonymously complete an online questionnaire. Questions related to diagnosis, treatment and potential role of the pharmacist. Answers were formulated as multiple-choice or ratings on a 5-point Likert scale. Data were analysed per professional group using descriptive statistics. Answers of pharmacists and GPs to corresponding questions were analysed using chi-square test ($p < 0.05$).

Main outcome measure

Desirability of patient-initiated treatment and supporting role of the pharmacist.

Results

A total of 170 GPs and 76 pharmacists completed the questionnaires. Of the GPs, 35.1% supported patient-initiated treatment. Of the pharmacists, 69.7% were willing to dispense an antibiotic to a patient without preceding GP consultation after a probability check. In total, 65.7% of GPs and 44.7% of pharmacists thought that facilitated access to antibiotics would increase use of antibiotics ($p < 0.05$).

Conclusion

Support of GPs for facilitated access to antibiotic treatment by patient-initiated UTI treatment was limited, even with pharmacist support. The majority of pharmacists were willing to dispense an antibiotic after a probability check of an episode of recurring UTI, but both pharmacists and GPs were concerned about overuse of antibiotics.

Introduction

Uncomplicated urinary tract infections (UTI) are among the most common acute conditions for women in primary care, with a lifetime prevalence of 40–60% [1, 2]. Most women experience their first UTI before age 25 [1]. A UTI is the most frequent indication for an antibiotic prescription in primary care in the Netherlands [3]. In most countries, women with recurring UTI require a prescription for an antibiotic.

The Dutch General Practitioners UTI guideline recommends that general practitioners (GPs) discuss the symptoms of recurring UTI and self-initiated treatment with their female patients. If patients recognize the symptoms, GPs can provide them with an antibiotic prescription to be filled "when needed" [4]. This patient-initiated treatment (PIT) is supported by a study finding that 84% of otherwise healthy women aged 18–51 years could accurately self-diagnose and self-treat recurring UTI [5].

4.1

To date, antibiotic use and bacterial resistance in the Netherlands are relatively low [6, 7]. These statistics may be attributable to relatively good adherence of GPs to the prescribing guidelines, which are reinforced by regular pharmacotherapeutic audit meetings between GPs and pharmacists [8]. As a prerequisite, facilitated access to UTI antibiotics for PIT should not increase bacterial resistance.

In many countries, treatment for chronic diseases is shifting from hospital to primary care, due to the aging of the general population and the increased length of time people live at home. As GPs and practice nurses face increasing workloads [9], pharmacist provision of treatment for minor ailments such as recurring UTI may relieve some of the burden for GPs and their practices. According to study findings, it is possible to shift appropriate care duties, such as a probability check of an episode of recurring UTI, from the GP to the community pharmacist [10].

In some Canadian provinces and in New Zealand, women with recurring UTI can consult a trained pharmacist to receive an antibiotic without a preceding physician prescription [10-12]. In the Netherlands, community pharmacists may advise patients on nonprescription medicines for minor ailments, but they are not allowed to dispense prescription-only medicines such as antibiotics

without a physician prescription. However, community pharmacists in the Netherlands may refill prescriptions if the physician has explicitly stated the number of times a prescription may be refilled [13].

Pharmacist support for women who choose to self-initiate treatment for UTI may provide GPs with additional confidence in this process. The resulting support of GPs for self-initiated treatment could enable a growing number of women to choose this option.

Aim of the study

The aim was to study the opinions of GPs and pharmacists regarding the desirability of patient-initiated treatment of recurring UTI. The potential role of the pharmacist in this process was studied, as were the potential consequences for antibiotic dispensing of facilitating access to antibiotics through patient-initiated treatment with pharmacist support.

Ethics Approval

This study was approved by the coordinator of the postgraduate workplace-based curriculum for community pharmacist specialists. Use of observational data in descriptive studies in the Netherlands is not considered to be an interventional trial, according to Directive 2001/20EC of Dutch legislation [14, 15]. Therefore, the study protocol did not need to be submitted to a medical ethics committee for approval.

Method

Study design and inclusion

A cross-sectional study was performed using an online survey for GPs and community pharmacists in the Netherlands. Data were collected between March and July 2018. Pharmacists from 76 pharmacies, all of whom were enrolled in a postgraduate education program to become community pharmacy specialists, recruited study participants. Each postgraduate trainee personally invited the residency pharmacist, and 2–3 general practitioners from practices in their regional primary care network to anonymously complete an online questionnaire.

Questionnaire design

Separate questionnaires were designed for GPs and pharmacists. The questionnaires were developed based on the findings of semi-structured face-to-face interviews with three GPs and three community pharmacists about procedures in GP-practice and PIT. The main topics addressed in the GP questionnaire included the current practice regarding diagnosis and treatment of recurring UTI and the ability of women to self-initiate treatment. In the pharmacist questionnaire, the main topics addressed were the willingness to check the probability of recurring UTI and implementation needs. Both questionnaires were piloted by two pharmacists and two GPs, respectively, to evaluate clarity and presentation and identify missing items. The questionnaires included questions with predefined options (with or without open response boxes) and statements to be ranked on a 5-point Likert scale that ranged from “totally disagree” to “totally agree”.

Data collection

The postgraduate trainees e-mailed the participating GPs and residency pharmacists a link to the questionnaire with a research code for identification of the questionnaire. The researchers had access to the submitted anonymized responses. Personal data were accessible to the postgraduate trainee only. The researchers communicated with the postgraduate trainees through the coordinator of the curriculum, who acted as a ‘trusted third person’. If needed, the GPs and supervising pharmacists received two reminders from the trainees to complete the questionnaire. The survey was conducted using an online survey system (Questback Version 27).

Data Analysis

Descriptive statistics were calculated, and answers were analysed for each professional group. For the Likert scale questions, a positive answer was calculated by adding “agree” and “totally agree” responses, a negative answer was calculated by adding “not agree” and “totally not agree” responses. Answers of pharmacists and GPs to corresponding questions were analysed using chi-square test ($p < 0.05$). All answers were analysed according to the gender and age of the respondents using chi-square test ($p < 0.05$). A cut-off of 45 years (median age of GPs and pharmacists) was used for age categories. Open responses were coded and counted and percentages were calculated. All data were analysed using IBM SPSS for Windows, version 23.0.

Results

Response

The questionnaires were completed by 76 community pharmacists and 170 GPs from practices cooperating with the pharmacies. Of all invited GPs, 25 did not complete the questionnaire. Table 1 shows the characteristics of GPs and pharmacists.

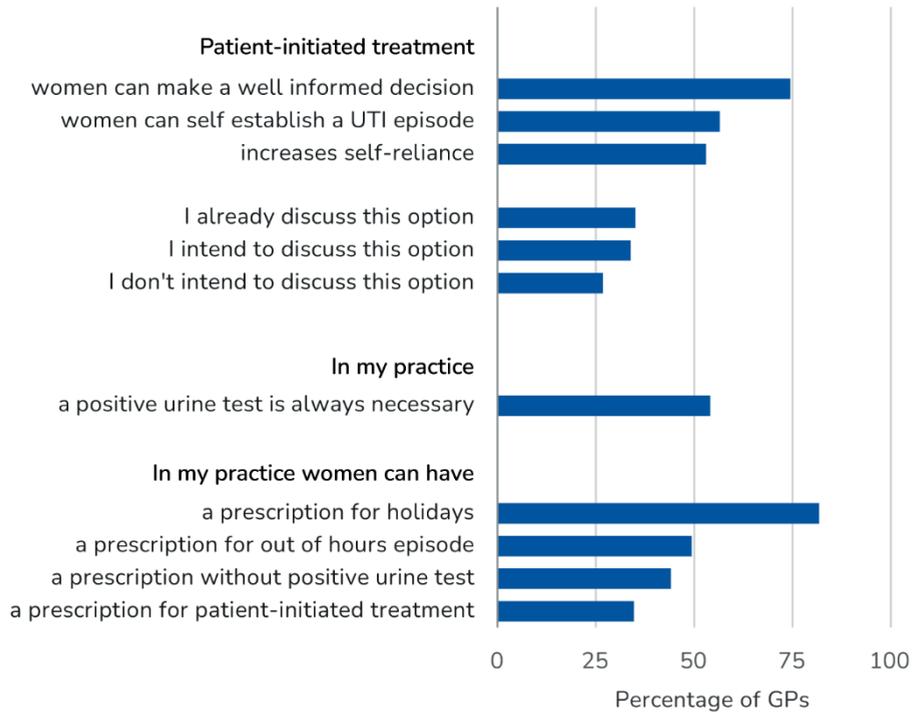
Table 1. Characteristics of community pharmacists and GPs

	Community pharmacists	GPs
Total number of participants (% of all pharmacists/GPs working in pharmacy/GP practice in 2018)	76 (3.8%)	170 (2.2%)
Number of female participants (% of all participants)	37 (48.7%)	92 (54.1%)
Mean age (in years \pm sd)	45.7 \pm 9.8	46.0 \pm 10.5
Number of participants 45 years or older	32 (42.1%)	77 (45.3%)

Opinions of GPs and pharmacists regarding self-initiated treatment and pharmacist support

As illustrated in Figure 1, 56.5% of GPs thought that women could self-diagnose a UTI episode. The majority of GPs (74.5%) agreed that women could self-initiate treatment, provided that the GP discussed the advantages and disadvantages of doing so with their patients. Of the GPs, 35.1% already discussed the possibility of PIT with their patients, whereas 26.8% of GPs had no intention of discussing this. Additionally, 34.7% of the GPs reported that women in their practice could already receive a prescription for PIT if they recognised UTI symptoms. Further, 82.9% of GPs reported that they would provide an antibiotic prescription to take for holidays if a female patients requested it.

Figure 1. Opinions of general practitioners regarding recurring urinary tract infection (UTI) and patient-initiated treatment



4.1

As illustrated in Table 2, 32.5% of GPs expected that pharmacists would be willing to check the probability of a recurring UTI episode. Significantly more pharmacists (69.7%) indicated that they would be willing to do this.

Table 2. Opinions of general practitioners (GPs) and community pharmacists regarding probability check of an episode of recurring urinary tract infections (UTI) by the community pharmacist.

	General practitioners n = 170	Community pharmacists n = 76	p-value
Willingness of pharmacists to check probability of an episode of recurring UTI *			< 0.05
Agree (total)	32.5% (54)	69.7% (53)	
Neutral	38.0% (63)	13.2% (10)	
Not agree (total)	31.9% (53)	17.1% (13)	
Accredited training program for pharmacists is necessary to be able to check the probability of an episode of recurring UTI			
Agree (total)	59.4% (101)	72.4% (55)	
Neutral	22.4% (38)	11.8% (9)	
Not agree (total)	18.2% (31)	3.0% (12)	
Expectation of increase in antibiotics dispensing*			< 0.05
Agree (total)	65.7% (109)	44.7% (34)	
Neutral	24.1% (40)	19.7% (15)	
Not agree (total)	10.2% (17)	35.5% (27)	
Pharmacist expects no objection from the cooperating GPs to pharmacists' probability check of an episode of recurring UTI, provided agreements are made			
Agree (total)	n/a	18.4% (14)	
Neutral	n/a	35.5% (27)	
Not agree (total)	n/a	46.1% (35)	
Pharmacists can support patients with recurring UTI with ^a :			
Information on preventive actions	68.6% (116)**	94.7% (72)**	< 0.05
Information on nonprescription medication	65.7% (111)**	80.3% (61)**	< 0.05
Referral to the GP for prophylaxis	53.3% (96)**	77.6% (59)**	< 0.05
GP conditions for probability check of episode of recurring UTI ^b :			
Agreements in pharmacotherapeutic audit meeting	67.1% (112)	n/a	
Pharmacist verification of symptoms	49.1% (82)	n/a	
Feedback on dispensing	68.9% (115)	n/a	
Pharmacist check of patient history	40.7% (68)	n/a	
Preference for organization of probability check in pharmacy*:			< 0.05
Care provided by pharmacist, with or without support from pharmacy assistant	45.9% (78)	19.7% (15)	
Care provided by pharmacy assistant with protocol after in-service training	30.0% (51)	59.2% (45)	
Care provided by pharmacy assistant with protocol	16.6% (18)	19.7% (15)	
Other	13.5% (23)		

^a total >100%; more than one answer allowed

* statistical significance of differences between matrices of agree, neutral and not agree for pharmacists and GPs tested by Chi-square test, difference significant if p<0.05

** statistical significance tested by Chi-square test, difference significant if p<0.05

Other options for pharmacist support

Additionally, 68.8% of GPs indicated that pharmacists could support women by offering advice on preventive actions to avoid UTI, and 94.7% of the pharmacists thought that they could provide this advice. Some 53.3% of GPs and 77.6% of pharmacists indicated that pharmacists could support women by determining their eligibility for prophylaxis. In the case of prescribing an antibiotic for recurring UTI, 47.1% of the GPs reported that they checked a patient's eligibility for prophylaxis by consulting the electronic patient record to determine the number of episodes in the previous 12 months.

Potential consequences of facilitated access to antibiotics with pharmacist support

Of the 170 GPs in the study group, 22.4% expressed concerns about losing information regarding their patients' antibiotic use, as well as the potential to miss alarm symptoms if women consult their pharmacist instead of the GP for a recurring UTI episode. Moreover, they felt responsible for diagnosing and prescribing. Of the pharmacists, 46.1% expected GPs to object to a probability check of a UTI episode by the pharmacist. If PIT for recurring UTI with pharmacist support were implemented, 65.7% of GPs and 44.7% of community pharmacists expected that there would be an increase in the number of dispensed antibiotics.

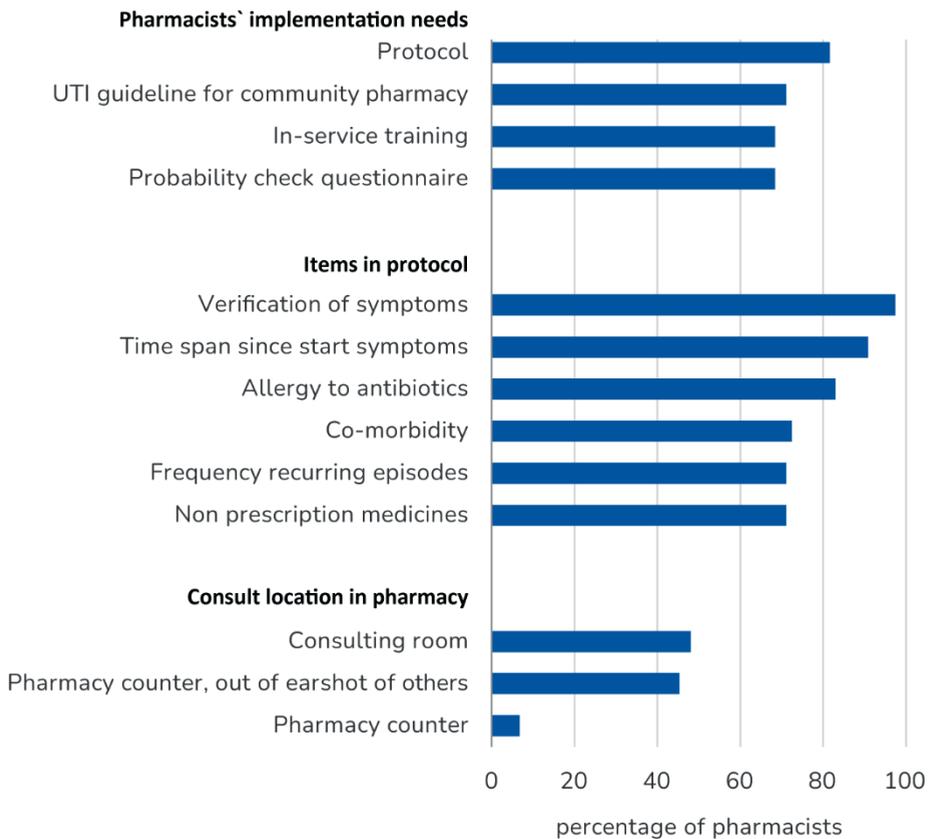
Organization and implementation in pharmacy

According to 59.4% of GPs and 72.4% of community pharmacists, an accredited training program for pharmacists should be mandated before they are allowed to check the probability of an episode of recurring UTI and dispense an antibiotic without a preceding consultation with the GP. In addition, 67.1% of the GPs emphasized the need to make sound agreements about prerequisites in a pharmacotherapeutic meeting. The question about the pharmacotherapeutic meeting was not in the community pharmacist questionnaire; however, 28.9% of pharmacists spontaneously reported a need for such agreements.

As illustrated in Figure 2, 81.6% of pharmacists reported that they would need a protocol to implement a probability check of an episode of recurring UTI and 68.4% would need a questionnaire to verify patient symptoms. Figure 2 also shows the items pharmacists would prefer in such a protocol. According to 45.9% of GPs and 19.7% of pharmacists, only the pharmacist should be

allowed to check the probability of an episode of recurring UTI (see Table 2). Additionally, 93.3% of the pharmacists thought that checking the probability of an episode of recurring UTI should take place out of the earshot of other patients in the pharmacy, and 48.0% of the pharmacists preferred a consulting room (see Figure 2).

Figure 2. Opinions of community pharmacists regarding pharmacy implementation of probability check of an episode of recurring urinary tract infection (UTI)



Gender and age of GPs and pharmacists

No significant gender-based differences were observed in the answers to the reported questions for GPs or community pharmacists. Additionally, no age-based differences were observed for either group based on the categories of <45 years and ≥45 years.

Discussion

Support of GPs for facilitated access to antibiotic treatment by patient-initiated UTI treatment was limited, even with pharmacist support. The majority of pharmacists was willing to check the probability of an episode of recurring UTI, but both pharmacists and GPs were concerned about overuse of antibiotics. Pharmacist-facilitated access to antibiotics was regarded feasible only if a number of conditions were met.

The majority of GPs thought that women could make a well-informed decision about PIT after discussing advantages and disadvantages with the GP. However, only one-third of the GPs had discussed PIT with their patients. Significantly more community pharmacists expressed willingness to check the probability of an episode of recurring UTI than expected by GPs. Additionally, significantly more GPs than pharmacists expected that the number of antibiotics dispensed would increase if pharmacists were to check the probability of recurring UTI. The most significant concerns mentioned by GPs in the study regarding PIT with pharmacist support were: (i) losing oversight of patients' antibiotic use, (ii) missing potentially alarming symptoms and (iii) feeling responsible for diagnosing and prescribing in case of an episode of recurring UTI.

Further, more than half of the GPs emphasized the need to make sound agreements about prerequisites. Pharmacists and general practitioners in the Netherlands have regular pharmacotherapeutic meetings, although on varying levels [16]. In practice, the extent of collaboration between pharmacists and GPs also varies. An earlier study found that attempts to encourage one professional group to expand or extend their practice may be perceived as a threat by members of the other group [17]. Clear communication and sufficient time to establish interprofessional trust are potential strategies to mitigate such perceptions [17, 18]. Barriers to effective interprofessional collaboration include perceived hierarchy and power imbalances between the professions and a lack of understanding of each party's skills and knowledge [19]. A systems thinking approach is supported by a study of a role swap of a pharmacist-led transfer of care [20]. A positive experience of collaboration with a member of the other party led to greater understanding of each group's capabilities and potential roles. Also, co-location and other resources to

facilitate clear and regular communication between the GP practice and the pharmacy team are important facilitators of interprofessional collaboration [18, 19]. Delegation of care to a pharmacy assistant or pharmacy technician should also be discussed since significantly more GPs expressed a preference for provision of care by the pharmacist. The education level of pharmacy assistants in practice varies from a basic three year vocational level training up to accredited (self)-care modules on top of this basic training. As of 2004, the pharmacy technician position was added to the pharmacy workforce. To become a pharmacy technician, experienced pharmacy assistants have to complete three years of additional training at the level of higher professional education, which includes theoretical courses and workplace learning [21]. All of these factors must be accounted for prior to implementing a probability check by a pharmacist. Potential GP objections to such practice could be mitigated through pharmacotherapeutic meetings that include discussion of these factors, sound agreements about prerequisites for antibiotic dispensing, monitoring and feedback of the number of antibiotic dispensings [8].

Half of the GPs in the study did not support PIT, most likely because they thought confirmation through a diagnostic urine test in the GP practice was necessary for initiation of UTI treatment. Doubts about women's health literacy and ability to establish whether they might have recurring UTI may contribute to this opinion. A pharmacy study in the Netherlands found that half of pharmacy visitors had limited health literacy skills, with health literacy being defined as the ability to obtain, understand and apply information to make appropriate health decisions [22]. PIT may prove difficult for women who have limited health literacy skills; however, pharmacist support through a probability check and clear communication may facilitate PIT for such women.

Unexpectedly, the majority of GPs in this study reported that they were willing to write a prescription in advance for female patients to take with them when they were going on holiday, though only half thought that women were able to self-diagnose a UTI episode. It is possible that GPs think only women who recognise symptoms will ask for a prescription for holidays. Additionally, women will only ask for such a prescription if they are aware that it is an option.

GPs' objections to pharmacists checking the probability of a UTI episode may also be related to the fact that antibiotic resistance in the Netherlands is

currently lower than in other countries [7], which is likely a consequence of close adherence to GP guidelines. More than 40% of pharmacists expected an increase in antibiotic dispensing. Consequently, prevention of overuse of antibiotics should be an important component of training programs, as well as tools such as guideline and protocol.

More than 70% of pharmacists in the study indicated that they would need a guideline and a training program for implementation. In Canada, a pharmacist UTI guideline was developed that includes symptoms, differential symptoms, co-morbidities and complicating factors [12]. A large prospective registry study indicated that trained pharmacists were able to use the pharmacist UTI guideline to assess and treat UTI in a comparable manner to physicians [10]. Pharmacist management of UTI proved to be highly effective and safe. The clinical cure rate in the Canadian study was 88.9%, and patients reported high satisfaction with this clinical service.

A pharmacist guideline may also be the basis for a protocol. A majority of pharmacists indicated a need for a symptom verification questionnaire as part of a protocol. Prior studies found that a diagnostic algorithm may be a reliable, safe and efficient method to check the probability of an episode of recurring UTI [23, 24].

Nearly 70% of GPs reported that pharmacists could support them by informing women about preventive actions. In GP practice, urine checks by a practice assistant are not usually followed by a GP consultation, and limited information is provided to patients regarding preventive actions.

Half of GPs mentioned that pharmacists could refer female patients to the GP if they seem eligible for prophylaxis. The GP guideline mentions prophylactic treatment and PIT as options for women who have three or more episodes of recurring UTI within a 12-month period [4]. Only half of GPs in this study checked the electronic patient record for the number of episodes in the preceding 12 months, which indicates that screening for viability of prophylactic or PIT is not systematically performed. In the Netherlands, pharmacists can systematically screen their pharmacy information system to determine a patient's eligibility for prophylaxis and for PIT.

Strengths and limitations

A strength of the study was that: (i) the practices of GPs and community pharmacists were distributed across the Netherlands, (ii) the practices were distributed over rural and urban areas and (iii) GPs and pharmacists in the study worked together in a regional care network. Another strength of the study is that the surveys were anonymous; anonymity increases the likelihood that healthcare providers expressed their true opinions. A limitation of the study is that the number of community pharmacists and GPs was relatively low compared to all community pharmacists and GPs in the Netherlands. Based on a comparison of the percentages of male and female GPs and pharmacists with national data, the group of GPs seems representative contrary to the pharmacists' group [25]. Another limitation is that we failed to ask the community pharmacists about their opinion regarding the conditions for the probability check. Some 70% of pharmacists agreed that an accredited training program is needed to be able to check the probability of an episode of recurring UTI. We did not acknowledge whether this need was for a training program for themselves or for other pharmacists.

Conclusion

The GPs in this study believed that female patients may recognise recurring UTI; however, they were reluctant to facilitate access to patient-initiated antibiotic treatment of recurring UTI, even with pharmacist support. The majority of pharmacists was willing to check the probability of an episode of recurring UTI. Pharmacist-facilitated access to antibiotics was determined to be a feasible alternative only if a number of conditions were met, including discussion of GP concerns, agreements with GPs, a pharmacist UTI guideline, a questionnaire for verification of symptoms and an accredited training program.

Acknowledgements

The authors thank the young pharmacist groups in the postgraduate workplace-based curriculum, as well as Caroline van de Steeg, PhD, coordinator of the EPA “Initiating, performing and/or taking part in practical research.” They also thank the GPs and community pharmacists who were willing to share their expertise in the questionnaires.

Funding

No funds, grants, or other support was received.

Conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author’s contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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Supplementary material

Table 1: Questionnaire Community Pharmacists

1 What information does your pharmacy provide to adult, non-pregnant women when antibiotics for uncomplicated UTI are dispensed? (Multiple answers allowed):	
Information about the antibiotic (effect, side-effects, way of use, etc.)	100% (76)
Information about uncomplicated UTI	32.9% (25)
Information about preventive actions	50.0% (38)
Information about OTC drugs	25.0% (19)
2 Do you receive prescriptions for self-initiated treatment in the pharmacy?	
Never	10.5% (8)
Rarely	28.9% (22)
Sometimes	53.9% (41)
Regularly	6.6% (5)
3 If you do get them, what enables you to distinguish these prescriptions from the usual prescriptions for uncomplicated UTI?	
Information from the GP on the prescription	35.5% (27)
Information from the woman	32.9% (25)
The woman has two prescriptions at the same time	11.8% (9)
Other; Combinations of the items mentioned before	7.9% (6)
Other; n/a	11.8% (9)
4 Self-initiated treatment allows a woman to take responsibility for the treatment of uncomplicated UTI	
Totally agree	22.7% (17)
Agree	52.0% (39)
Neutral	12.0% (9)
Not agree	9.3% (7)
Totally not agree	4.0% (3)
5 Self-initiated treatment allows a woman to consider treatment without an antibiotic	
Totally agree	9.3% (7)
Agree	41.3% (31)
Neutral	18.7% (14)
Not agree	26.7% (20)
Totally not agree	4.0% (3)
6 Which of the following would you perform to support women with episodes of recurring UTI without preceding consultation with the GP:	
Information about preventive actions	94.7% (72)
Information about OTC drugs	80.3% (61)
Referral to the GP in case of insufficient effect of an antibiotic	82.9% (63)

Referral to the GP for prophylaxis	77.6% (59)
Referral to GP if I doubt it to be a UTI episode	78.9% (60)
Check on suitability of an antibiotic in pregnancy, use of other medication, comorbidity or allergy	89.5% (68)
Other; Effective use	1.3% (1)

7 | Which of the following statements best applies to the organisation of care in your pharmacy for women with episodes of recurring UTI without preceding consultation with the GP:

I as a pharmacist provide this care	7.9% (6)
I validate the episode, counsel the woman and check the medication record, while a pharmacy assistant dispenses	11.8% (9)
A pharmacy assistant can provide this care after training, using a protocol	59.2% (45)
A pharmacy assistant can provide this care using a protocol	19.7% (15)
Other	1.3% (1)

8 | What supplementary information do you need for the support of a woman with an episode of recurring UTI without preceding consultation with the GP?

A diagnostic urine test	55.3% (42)
Information from the GP that they have discussed this change	90.8% (69)
Complaints of the woman	71.1% (54)
Frequency of episodes	71.1% (54)
Comorbidity	60.5% (46)
Use of OTC drugs	56.6% (43)
Other; Diagnosis of recurring UTI	2.6% (2)

9 | Pharmacists need accredited training before being allowed to validate an episode of recurring UTI and dispense an antibiotic without preceding consultation with a GP

Totally agree	27.6% (21)
Agree	44.7% (34)
Neutral	11.8% (9)
Not agree	11.8% (9)
Totally not agree	3.9% (3)

10 | Which of the following should be included in a protocol for support of women with episodes of recurring UTI without preceding consultation with the GP (Multiple answers allowed):

Verification of complaints (pain or burning when passing urine, frequent urination, urgent urination of small volumes or urine, blood seen in urine, fever, vaginal discharge etc.)	97.4% (74)
How long have the complaints been bothering the woman	90.8% (69)
How long since the previous episode of uncomplicated UTI	92.1% (70)
Comorbidity	72.4% (55)
Comedication	71.1% (54)

Allergy to an antibiotic	82.9% (63)
Information about use of OTC drugs e.g. cranberry, d-mannose or vitamin C	71.1% (54)
Other; Impaired renal function	2.6% (2)
11 Does your pharmacy have a consulting room?	
Yes	96.1% (73)
No	2,6% (2)
Other	1.3% (1)
12 Where should a consultation with a woman about an episode of recurring UTI without preceding consultation with the GP take place?	
Should take place in a consulting room	48.0% (36)
Can take place at a pharmacy counter that has sufficient privacy and is out of earshot of other patients	45.3% (34)
Can take place at a pharmacy counter	6.7% (5)
13 What do you need for a consultation with a woman about an episode of recurring UTI without preceding consultation with the GP?	
UTI guideline for pharmacists	71.1% (54)
In-service training	68.4% (52)
Protocol	81.6% (62)
Supporting materials for pharmacotherapeutic audit meeting with GPs	32.9% (25)
Questionnaire for the women (e.g. about complaints)	68.4% (52)
Information materials for women about UTI, treatment, self-care and preventive actions	61.8% (47)
Nothing, you can use the GP guideline	9.2% (7)
Other; Agreement with GP and continuous GP prescription	2.6% (2)
14 I am willing to take responsibility for the validation of and dispensing of an antibiotic for an episode of recurring UTI without preceding consultation with the GP.	
Totally agree	23.7% (18)
Agree	46.1% (35)
Neutral	13.2% (10)
Not agree	11.8% (9)
Totally not agree	5.3% (4)
15 I foresee an increase in use of antibiotics, and therefore of antibiotic resistance, if antibiotics for recurring UTI become available without preceding consultation with a GP.	
Totally agree	7.9% (6)
Agree	36.8% (28)
Neutral	19.7% (15)
Not agree	28.9% (22)
Totally not agree	6.6% (5)

16 | I foresee no objections from the GPs, with whom I cooperate, about the validation of episodes of recurring UTI and dispensing of antibiotics without preceding consultation with the GP in pharmacy, provided good agreements are made beforehand.

Totally agree	(0)
Agree	18.4% (14)
Neutral	35.5% (27)
Not agree	34.2% (26)
Totally not agree	11.8% (9)

17 | Age

18 | Gender

Female	51.3% (39)
Male	48.7% (37)

19 | What is your position in pharmacy (Multiple answers allowed)

Owner	22.4% (17)
Co-owner	11.8% (9)
Managing pharmacist	68.4% (52)
Locum pharmacist	9.2% (7)

Table 2: Questionnaire General Practitioners

1 If a patient has complaints of an episode of recurring UTI she	
can have her urine tested in the GP practice in the morning before a certain time	33.5% (57)
can have her urine tested in the GP practice all day	60.0% (102)
can have her treatment after a consult by phone, if she recognises the complaints	6.5% (11)
2 As well as having her urine tested, the patient must fill in a form with questions about the complaints and comorbidities	
Yes	62.4% (106)
No	25.9% (44)
Other, the practice assistant asks for complaints	11.8% (20)
3 If yes, are questions asked about the use of OTC medication?	
Yes	12.7% (13)
No	87.3% (89)
4 Are the activities of the GP practice assistant based on a UTI protocol?	
Yes, which has been developed in this GP practice	13.5% (23)
Yes, which is available on the website of NHG, the Dutch GP association	21.2% (36)
Yes, which has been derived from the NHG protocol	61.8% (105)
No, the practice assistant does not work according to a protocol	3.5% (6)
5 If the diagnostic test result is positive, what happens before approval of the prescription by the GP (Multiple answers allowed):	
The practice assistant prepares the prescription in the electronic prescribing system	48.8% (83)
The practice assistant consults the GP about inviting the woman for a GP consultation	27.1% (46)
The practice assistant checks her data in the electronic patient file	2.4% (4)
The GP checks her data in the electronic patient file	50.0% (85)
The GP only checks data in the electronic patient file for complex patients only	22.9% (39)
The GP checks the number of UTI episodes in the previous 12 months	47.1% (80)
6 A positive diagnostic urine test is necessary before prescription of an antibiotic for an episode of recurring UTI	
Totally agree	12.9% (22)
Agree	41.2% (70)
Neutral	14.1% (24)
Not agree	27.6% (47)
Totally not agree	4.1% (7)
7 An antibiotic can be prescribed without a positive diagnostic test if a woman has evident complaints of an episode of recurring UTI out of hours	
Totally agree	15.9% (27)
Agree	58.8% (100)
Neutral	17.1% (29)
Not agree	11.8% (20)

1	Totally not agree	1.8% (3)
8	In theory, patients could perform a diagnostic urine test with a dipstick	
	Totally agree	7.6% (13)
	Agree	40.0% (68)
	Neutral	23.5% (40)
	Not agree	25.3% (43)
	Totally not agree	3.5% (6)
9	Women can assess an episode of recurring UTI based on their complaints, provided that the GP has previously diagnosed an uncomplicated UTI	
	Totally agree	4.1% (7)
	Agree	52.4% (89)
	Neutral	18.8% (32)
	Not agree	22.4% (38)
	Totally not agree	2.4% (4)
10	Women who are able to assess an episode of recurring UTI based on their complaints, in my GP practice (multiple answers allowed):	
	They receive a prescription without diagnostic urine test	43.5% (74)
	They receive a prescription for self-initiated treatment	32.9% (56)
	They receive a prescription for complaints in the evening, at night or on the weekend	49.4% (84)
	They receive a prescription for an antibiotic to take with them when going on holiday (if they ask for one)	81.8% (139)
11	A woman having an episode of recurring UTI can await progress of complaints for 24-48 hours with ample fluid intake and use of painkillers, without any problems.	
	Totally agree	14.9% (25)
	Agree	58.9% (99)
	Neutral	17.3% (29)
	Not agree	8.9% (15)
	Totally not agree	(0)
12	Self-initiated treatment enables women to start antibiotic treatment more quickly.	
	Totally agree	10.7% (18)
	Agree	57.4% (97)
	Neutral	19.5% (33)
	Not agree	12.4% (21)
	Totally not agree	(0)
13	Self-initiated treatment of recurring UTI allows women to take responsibility for the treatment of their complaints.	
	Totally agree	3.6% (6)
	Agree	49.4% (83)

Neutral	26.2% (44)
Not agree	19.6% (33)
Totally not agree	1.2% (2)
14 Self-initiated treatment of recurring UTI allows women to consider treatment without an antibiotic.	
Totally agree	8.9% (15)
Agree	32.0% (54)
Neutral	24.3% (41)
Not agree	30.8% (52)
Totally not agree	4.1% (7)
15 A woman can take an informed decision to start self-initiated treatment, provided that the GP discusses with her the advantages and disadvantages.	
Totally agree	8.5% (14)
Agree	66.1% (109)
Neutral	17.6% (29)
Not agree	7.9% (13)
Totally not agree	(0)
16 Which of the following would you expect the pharmacist to use to support a woman with an episode of recurring UTI without preceding consultation with the GP:	
Information about preventive actions	68.6% (116)
Information about OTC drugs	65.7% (111)
Referral to the GP in case of insufficient effect of an antibiotic	66.3% (112)
Referral to the GP for prophylaxis	53.3% (90)
Referral to GP if an episode of u-UTI is not evident	73.4% (124)
Check on suitability of an antibiotic in pregnancy, use of other medication, comorbidity or allergy	77.5% (131)
17 Which of the following best describes the preferred organisation of care in pharmacy for women with an episode of recurring UTI without preceding consultation with a GP:	
The pharmacist must provide this care	19.7% (29)
A pharmacy technician can support the pharmacist by gathering information from the woman about the complaints and by dispensing activities	19.7% (29)
The pharmacist should validate the episode, counsel the woman and check the medication record	13.6% (20)
A pharmacy technician can provide this care after training, using a protocol	34.7% (51)
A pharmacy technician can provide this care using a protocol	12.2% (18)
18 Which of the following topics should be included in a protocol for supporting women with an episode of recurring UTI without preceding consultation with the GP (Multiple answers allowed):	

Verification of complaints (pain or burning when passing urine, frequent urination, urgent urination of small volumes or urine, blood seen in urine, fever, vaginal discharge etc.)	77.8% (130)
How long the complaints have been bothering the woman	64.1% (107)
How long since the previous episode of UTI	71.3% (119)
Frequency of UTI episodes in the preceding 6 or 12 months	82.6% (138)
Comorbidity	87.4% (146)
Comedication	51.5% (86)
Allergy to an antibiotic	77.2% (129)
Information about use of OTC drugs e.g. cranberry, d-mannose or vitamin C	24.0% (40)
Other; Sexual Transmitted Disease (STD) risk	4.2% (7)
Other; Feedback to GP	1.8% (3)

19 | Under what circumstances can a pharmacist take responsibility for validation of an episode of recurring UTI and dispensing of an antibiotic without preceding consultation with a GP (Multiple answers allowed)?

A diagnostic urine test is performed	28.1% (47)
If the pharmacist verifies the complaints	49.1% (82)
If the pharmacist consults the patient history and approves the dispensing of an antibiotic	40.7% (68)
If the pharmacist provides the GP with feedback about dispensed antibiotics	68.9% (115)
If arrangements have been agreed on in the pharmacotherapeutic audit meeting	67.1% (112)

20 | Pharmacists need accredited training before they can validate an episode of recurring UTI and dispense an antibiotic without preceding consultation with a GP

Totally agree	25.0% (40)
Agree	38.1% (61)
Neutral	17.5% (28)
Not agree	5.6% (9)
Totally not agree	13.8% (22)

21 | For the validation of an episode of recurring UTI without preceding consultation with a GP, the pharmacist must conform to the current GP UTI guideline.

Totally agree	54.8% (91)
Agree	36.1% (60)
Neutral	3.6% (6)
Not agree	(0)
Totally not agree	5.4% (9)

22 | Which of the following situations applies to you?

When a patient has episodes of recurring UTI, and they are able to recognise the complaints, I talk to them about the option of self-initiated treatment	36.2% (60)
I intend to discuss the option of self-initiated treatment with patients who have episodes of recurring UTI, and are able to recognise the complaints	35.5% (59)

I don't intend to discuss the option of self-initiated treatment with patients who have episodes of recurring UTI, and are able to recognise the complaints,	28.3% (47)
23 I foresee no objections from the pharmacist(s), with whom I cooperate, to the validation of an episode of recurring UTI and dispensing of an antibiotic without preceding consultation with the GP.	
Totally agree	6.6% (11)
Agree	25.9% (43)
Neutral	35.5% (59)
Not agree	16.9% (28)
Totally not agree	15.1% (25)
24 I foresee an increase in use of antibiotics, and therefore of antibiotic resistance, if antibiotics for recurring UTI become available without preceding consultation with a GP.	
Totally agree	18.1% (30)
Agree	47.6% (79)
Neutral	24.1% (40)
Not agree	9.6% (16)
Totally not agree	0.6% (1)
25 Age	
26 Gender	
Female	54.1% (92)
Male	43.5% (74)
Missing	2.4% (4)
27 Kind of GP practice	
Solo	33.5% (57)
Duo	28.2% (48)
Group	38.2% (65)
28 Which of the following describes the GP practice?	
Inside a health centre	31.8% (54)
A GP practice and pharmacy under one roof	28.2% (48)
A GP practice and pharmacy in different locations	40.0% (68)

CHAPTER 4.2

Innovative Care from the Community Pharmacist: A consultation for women on prevention of recurring UTI: A survey study

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Nieuwe zorgverlening door de openbaar apotheker: een consultgesprek met vrouwen over preventie van blaasontsteking.

Nederlands Platform voor Farmaceutisch Onderzoek. 2022;7:a1758.

<https://www.knmp.nl/resolveuid/fb50c9c3bd9e400cb56074988d9b293a>

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Abstract

Background

Pharmacists are highly accessible and trusted healthcare professionals. In the Netherlands, counselling on the prevention of urinary tract infection (UTI) in community pharmacies is not yet common practice.

Objective

To study the willingness and ability of community pharmacists to counsel women on the prevention of UTI and identify facilitators and barriers for implementing this counselling.

Setting

Practicing community pharmacists affiliated with the Utrecht Pharmacy Practice network for Education and Research (UPPER)

Method

Community pharmacists were invited to complete an online questionnaire. Data were analysed using descriptive statistics.

Main outcome measure

Willingness and ability of community pharmacists to counsel women on preventing UTI and facilitators and barriers for implementation in pharmacies

Results

The questionnaire was completed by 78 pharmacists: 87.2% thought they were able, and 82.1% were willing to counsel women about UTI preventive actions. For implementation, 88.5% required patient information (brochure or website), 70.5% required a protocol, and 60.3% required training on UTI treatment and prevention. Training should include counselling techniques according to 82.1% and should be mandatory according to 42.3%.

Conclusion

Most community pharmacists thought they were competent and willing to counsel women about UTI prevention; however, additional training in counselling is needed.

Introduction

Uncomplicated urinary tract infections (UTIs) are among the most common acute female health conditions in primary care [1]. Almost half of women experience a recurring UTI at least once, with a recurrence risk of 30-50% per year [2]. Recurring UTI may be bothersome as women often require a positive urine test before antibiotics are prescribed [3]. Moreover, the high frequency of recurring UTIs contributes to clinical practice workload [4].

Education about behavioural risk factors may prevent UTI recurrence [4]. The Dutch GP UTI Guideline advises general practitioners (GPs) to discuss preventive management approaches with women who visit the general practice for UTI symptoms [3]. Earlier research has shown that women's knowledge of preventive actions varies with much room for improvement [5].

Risk factors for UTI recurrence are classified into four categories: (i) factors that impact the urogenital flora (e.g. frequent antibiotic use, personal hygiene, spermicide use, diaphragm and pessary use, and menopause), (ii) factors that facilitate bacterial entry into the bladder (e.g. sexual intercourse, frequent catheterisation and menopause), (iii) factors that decrease bacterial removal (e.g. decreased fluid intake, delayed voiding, incomplete bladder emptying, and pelvic organ prolapse), and (iv) factors that impair the immune response (e.g. diabetes, immunosuppressant use, tobacco use, and HIV/AIDS) [6].

Previous research has shown that women who prefer not to take antibiotics appreciate alternative management approaches and prevention advice [7]. Thus, the 2019 Dutch GP guideline recommends ample fluid intake (up to 3 litres a day), complete emptying of the bladder, not postponing micturition, emptying the bladder soon after sexual intercourse, and prophylactic use of cranberry or d-mannose to prevent recurrence of UTI [3].

Interventions encouraging effective self-management could decrease pressure on primary healthcare services and support targets for reducing antibiotic prescribing [8]. Healthcare providers can discuss with women practical ways to prevent and self-manage an episode of recurring UTI, advising them on improvements to decrease UTI episodes and the number of antibiotics prescribed for recurring UTIs.

According to the International Pharmaceutical Federation (FIP), pharmacists should engage in preventive care activities that promote public health and prevent disease [9]. Moreover, a general guideline on pharmaceutical counselling was developed for community pharmacists, based on the medical Calgary-Cambridge model, with recommendations for dispensing and self-care [10]. As GPs and practice assistants already encounter increasing workloads [4], pharmacist counselling on preventing UTI recurrence might relieve the burden for GP practices.

Aim of the study

To study the willingness and ability of community pharmacists to counsel women about prevention of recurring UTI, also assessing facilitators and barriers to implementing counselling

Ethics approval

This study was approved by the Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University (UPF1901).

Methods

A cross-sectional study was performed using an online survey for community pharmacists in the Netherlands. In a monthly electronic newsletter, practising community pharmacists affiliated with UPPER were invited to complete an online questionnaire anonymously [10]. Of all Dutch community pharmacies, 65% (1295 of 2000) are affiliated with UPPER [11].

Main questionnaire topics were willingness and self-assessed ability to perform UTI prevention counselling and pharmacists' needs to implement such counselling in daily practice. Moreover, general pharmacist and pharmacy characteristics were collected. The questionnaire included questions with predefined options (with or without open-response boxes) and statements ranked on a 5-point Likert scale, ranging from 'totally disagree' to 'totally

agree'. The questionnaire was piloted for clarity, presentation, and missing items by four community pharmacists.

Questionnaires were completed online via LimeSurvey (limesurvey.org). Data were stored on Utrecht University secure servers and were collected between September and November 2019.

Descriptive statistics were calculated. For the Likert scale questions, a positive answer was calculated by adding 'agree' and 'totally agree' responses, and a negative answer was calculated by adding 'not agree' and 'totally not agree' responses. All data were analysed using IBM SPSS for Windows, version 23.0.

Results

The questionnaire was completed by 78 community pharmacists. The median age was 40.5 years (ranging between 26 and 67 years), and 73.1% were women.

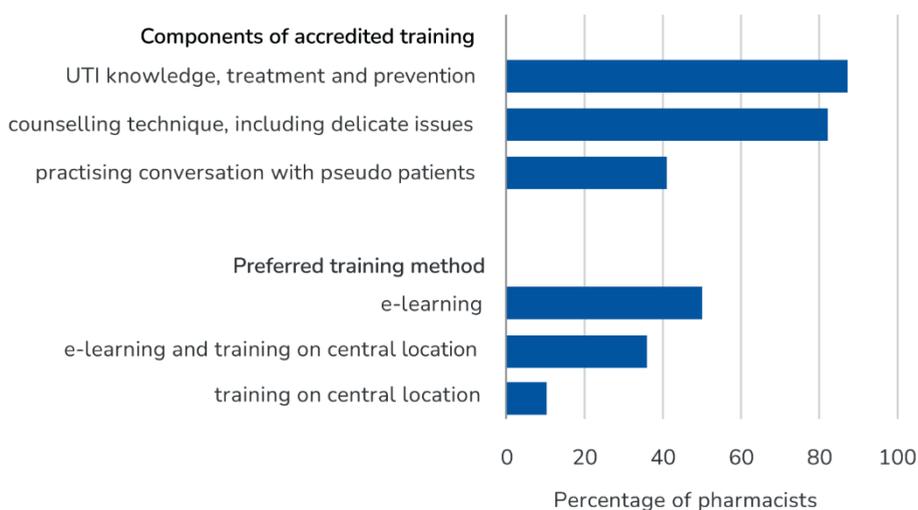
Table 1. General characteristics of community pharmacists

	Number of pharmacists <i>n</i> = 78
Women, n (%)	57 (73.1%)
Median age in years (range)	40.5 (26-67)
Function, n (%)	
owner	24 (30.8%)
pharmacy manager	28 (35.9%)
locum pharmacist	26 (33.3%)
Establishment, n (%)	
health centre (GP, pharmacy, other healthcare providers)	32 (41.0%)
GP and pharmacy in the same building	8 (10.3%)
single pharmacy	38 (48.7%)
Type of pharmacy, n (%)	
chain pharmacy	16 (20.5%)
independent pharmacy (incl. franchising formula)	62 (79.5%)
Location, n (%)	
town ≥ 100,000 inhabitants	21 (26.9%)
town ≤ 100,000 inhabitants	23 (29.5%)
village or countryside	34 (43.6%)
Regular pharmacotherapy meetings with GPs, n (%)	
without concrete agreements	14 (17.9%)
with concrete agreements	33 (42.3%)
with an evaluation of agreements	31 (39.7%)

Of the participants, 82.1% were willing to counsel women about UTI and preventive actions. Concerning knowledge about the subject and counselling competencies, 87.2% of pharmacists thought they were competent to counsel female patients. According to 78.2% of the pharmacists, some pharmacy assistants also had sufficient skills to counsel women on UTI, and, according to 10.3% of the participating pharmacists, all pharmacy assistants had these competencies.

Of the pharmacists, 56.4% expected no objections from the GPs concerning pharmacists counselling women about preventing recurring UTI. Fear of losing control (33.3%) and the fact that GPs and their practice assistants already informed women about preventive behavioural actions (38.5%) were the most frequently mentioned objections. Less frequently, pharmacists expected that GPs felt uncomfortable with the idea of the pharmacist counselling the patient (17.9%) and that GPs lacked confidence in the pharmacist's knowledge and expertise (14.1%).

Figure 1. Opinion of community pharmacists about accredited training for prevention counselling for women with recurring UTIs



According to 42.3% of pharmacists, accredited training for pharmacists should be obligatory before counselling on UTI prevention. As illustrated in Figure 1, 82.1% of pharmacists thought that counselling about hygienic behavioural actions and sexual intercourse should be part of the training programme.

Moreover, 41.0% of pharmacists believed that practising with pseudo-patients should be part of a training programme.

Pharmacists especially needed patient information on UTI in a brochure or website, a counselling protocol, and UTI treatment and prevention training to successfully implement UTI counselling (Table 2). Moreover, 26.9% spontaneously mentioned remuneration from a healthcare insurer, 17.9% mentioned attention to privacy and a consulting room, and 3.8% mentioned agreement with the GP on the eligibility of women and the topics to be discussed during counselling. Regarding the consultation location, most pharmacists thought the consulting room and the counter beyond hearing distance of other clients were most appropriate, whereas 3.8% spontaneously mentioned that this choice should be left to the client. The median time pharmacists thought they needed for prevention counselling was approximately 8 minutes, whereas more than one-third thought 10 minutes was needed.

Table 2. Opinion of community pharmacists about implementing prevention counselling for recurring UTIs in a pharmacy

	Number of pharmacists <i>n</i> = 78
Items needed for implementation in pharmacy, n (%)	
patient information, in brochure or website	88.5% (69)
protocol	70.5% (55)
materials for pharmacotherapeutic GP meeting	25.6% (20)
training on UTI treatment and prevention	60.3% (47)
Preferred timing of prevention counselling, n (%)	
1st dispensing, possibly repeated at 2nd dispensing	40.7% (24)
2nd dispensing, possibly repeated at next dispensing	53.9% (42)
every repeated dispensing of UTI antibiotics	12.8% (10)
Preferred person for prevention counselling, n (%)	
pharmacist	12.8% (10)
pharmacist first, pharmacy assistant later	23.1% (18)
pharmacy assistant after training	35.9% (28)
pharmacy assistant using a protocol	26.9% (21)
Counselling location, n (%)	
consulting room	59.0% (46)
counter, beyond other clients' hearing distance	35.9% (28)
counter	1.3% (1)
Estimated time needed for prevention counselling	
Median, in minutes (min-max)	8.0 (2-15)

Discussion

Most community pharmacists were willing and felt capable to counsel women about UTI prevention. However, almost half thought that additional training should be mandatory before they could perform counselling. Moreover, over half of the responding pharmacists would delegate prevention counselling to a pharmacy assistant, while a quarter wanted first to counsel female patients about prevention themselves upon implementing this new pharmacy service, then later delegate it to a pharmacy assistant.

For implementation in daily pharmacy practice, this last option is preferable because it enables the pharmacist to evaluate the implementation of UTI counselling before delegating it to a pharmacy assistant. Moreover, it enables the pharmacist to evaluate the pharmacy assistants and technicians best-equipped to counsel women on UTI prevention. The educational level of pharmacy assistants in practice varies from a basic three-year vocational level training to additional accredited (self)-care modules on top of this training. Notably, the pharmacy technician position was added in 2004 to the pharmacy workforce, requiring experienced pharmacy assistants to complete three years of additional training at a higher level of professional education, including theoretical courses and workplace learning [12].

Approximately half of the pharmacists did not expect objections from GPs, which may result from good interprofessional collaboration and trust [13]. Other contributing factors may have included that 80% of the pharmacists had regular pharmacotherapeutic meetings with GPs to agree on prescribing policy, and half of the pharmacies were located in the same building as the GPs [13].

Furthermore, 80% of the pharmacists thought counselling techniques should be part of a training programme, but fewer pharmacists (40%) valued practising with pseudo-patients during this training. However, this second option seems preferable because theoretical training, followed by small group training sessions with (simulated) patients, has previously improved communication skills effectively [14]. Skills development using role-play also might help pharmacists learn to counsel female patients about UTI prevention within a limited time frame.

Half of the pharmacists thought the preferred timing for prevention counselling was the second time a woman required a UTI antibiotic. This timing would align well with the information about risk factors for recurring UTI that patients are likely to receive from their GPs [3]. The pharmacist can start by asking women what information they retained from their GP visit and then provide the missing information.

However, pharmacists may be reluctant to provide counselling on UTI prevention without reimbursement. Moreover, community pharmacists rank the provision of cognitive pharmacy services as important [11]. Community pharmacists who spend more time on cognitive pharmacy services devote less time to managerial activities, logistics, and other activities [14]. These activities can be delegated to supporting staff members, but funding is necessary.

Strengths and limitations

A strength of the study is that the survey was anonymous, increasing the likelihood that healthcare providers expressed their true opinions. A limitation is the relatively low number of participants related to community pharmacists with a newsletter subscription. The low number of participants also hindered subgroup analyses.

Another limitation is that this group of pharmacists may not have been representative of all Dutch pharmacists (e.g. gender, function, pharmacy type). Moreover, considering the UPPER target audience, the number of pharmacists that provided patient-centred care might have been higher than average. Thus, a quantitative study with more respondents or a qualitative study into the pharmacists' motivations to counsel women about preventing UTI recurrence, enabling factors, and barriers may provide additional information about the feasibility of prevention counselling.

Conclusion

Most community pharmacists were willing to counsel female patients about UTI prevention and thought they were competent to perform it. However, training in conversation techniques and development of education materials deserve attention. Most pharmacists preferred a consultation room or the counter beyond hearing distance of other clients. It is preferable that

pharmacists and GPs discuss objections from GPs in pharmacotherapeutic meetings.

Acknowledgements

The authors thank Daphne Philbert, a research and education assistant at UPPER, and community pharmacists who supported the questionnaire's pilot.

Funding

This research did not receive a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest.

Author's contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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Supplementary material

Table 1: Questionnaire Prevention Consultation

1 I am willing to provide consultations for women who have episodes of recurring UTI and discuss their knowledge of risk factors and preventive actions (e.g. emptying of the bladder, sexual intercourse, use of nonprescription medicines such as cranberry and d-mannose)	
Totally agree	28 (35.9%)
Agree	36 (46.2%)
Neutral	11 (14.1%)
Not agree	3 (3.8%)
2 I am able to provide consultations for women who have episodes of recurring UTI and discuss their knowledge of risk factors and preventive actions (e.g. emptying of the bladder, sexual intercourse, use of nonprescription medicines such as cranberry and d-mannose)	
Totally agree	28 (35.9%)
Agree	40 (51.3%)
Neutral	7 (9.0%)
Not agree	3 (3.8%)
3 My assistants are able to provide consultations for women who have episodes of recurring UTI and discuss their knowledge of risk factors and preventive actions (e.g. emptying of the bladder, sexual intercourse, use of nonprescription medicines such as cranberry and d-mannose)	
Yes, all of my assistants	8 (10.3%)
Yes, some of my assistants	61 (78.2%)
No	9 (11.5%)
4 Which of the following best describes the preferred timing of counselling for prevention (Multiple answers allowed):	
At a first dispensing of a UTI antibiotic	10 (12.8%)
At a first dispensing with iteration at a second dispensing	14 (17.9%)
At a second dispensing	7 (9.0%)
At a second dispensing and iteration at each following dispensing	17 (21.8%)
At each following dispensing	10 (12.8%)
Not applicable; This is the GP's responsibility	2 (2.6%)
5 Which of the following best describes the preferred person for counselling for prevention :	
The pharmacist provides counselling for prevention	10 (12.8%)
A pharmacy assistant provides counselling for prevention after training	28 (35.9%)
A pharmacy assistant provides counselling for prevention using a protocol	21 (26.9%)
Firstly, the pharmacist provides counselling for prevention; at a later stage, a pharmacy assistant provide counselling for prevention	18 (23.1%)

Other, namely just based on our knowledge, not based on the umpteenth protocol	1 (1.3%)
--	----------

6 | Practical experience with counselling according to the KNMP guideline

Consulting is necessary for provision of counselling for prevention

Totally agree	15 (19.2%)
Agree	40 (51.3%)
Neutral	14 (17.9%)
Not agree	8 (10.3%)
Totally not agree	1 (1.3%)

7 | Where should counselling for prevention take place?

Should take place in consulting room	46 (59.0%)
Can take place at a pharmacy counter that has sufficient privacy and is out of earshot of other patients	28 (35.9%)
Can take place at a pharmacy counter	1 (1.3%)
Other, namely patient's preference	3 (3.8%)

8 | The pharmacist needs accredited training before being allowed to counsel for prevention

Totally agree	9 (11.5%)
Agree	24 (30.8%)
Neutral	28 (35.9%)
Not agree	15 (19.2%)
Totally not agree	2 (2.6%)

When answer to question 8 was (totally) agree or neutral:

9 | Which of the following should be included in accredited training (Multiple answers allowed)

Knowledge, treatment and prevention of UTI	68 (87.2%)
Counselling technique, including delicate issues	64 (82.1%)
Practising conversation skills with simulated patients	32 (41.0%)
Other; How best to share knowledge with team; Not applicable when consultation guideline is implemented	2 (2.6%)

10 | Which of the following would be your preferred training method

e-learning	39 (50.0%)
Training on a central location	8 (10.3%)
Blended learning	28 (35.9%)
Other; Tutorial; Do not know	3 (3.8%)

11 | What do you need for implementation of counselling for prevention in pharmacy (Multiple answers allowed)

Patient information, in writing	61 (78.2%)
---------------------------------	------------

Patient information website	45 (57.7%)
Protocol	55 (70.5%)
Materials for pharmacotherapeutic meeting	20 (25.6%)
Knowledge/ skills training	47 (60.3%)
Nothing	2 (2.6%)
Other; GP information; Remuneration; Patient awareness that prevention can be discussed with the pharmacist	3 (3.8%)

12 | Estimated time needed for counselling for prevention

13 | I do not expect objections from GPs to counselling of women for UTI risk factors and preventive actions in pharmacy

Totally agree	12 (15.4%)
Agree	32 (41.0%)
Neutral	20 (25.6%)
Not agree	12 (15.4%)
Totally not agree	2 (2.6%)

When answer to question 10 was neutral or (totally) disagree:

14 | Which of the following may be objections from the GP (Multiple answers allowed)

Fear of losing control	26 (33.3%)
GP provides information about prevention at the first UTI consultation	18 (23.1%)
Practice assistant provides information about prevention	12 (15.4%)
Feeling uncomfortable with the idea of the pharmacist counselling	14 (17.9%)
Financial reasons	5 (6.4%)
Lack of confidence in pharmacists' knowledge and expertise	11 (14.1%)
Pharmacist – GP relationship	3 (3.8%)
Other; No awareness of each other's knowledge and skills	1 (1.3%)

15 | Do you impose any other conditions for counselling for prevention? (Open question)

Remuneration	21 (26.9%)
Patient's consent	5 (6.4%)
Privacy/ consulting room	14 (17.9%)
Active announcement of this service	5 (6.4%)
Agreement with regional GPs about selection of patients and information to be provided	3 (3.8%)
Logistic process in the pharmacy in order	4 (5.1%)
GP practice assistant referring patients to the pharmacist	2 (2.6%)

Pharmacy characteristics

16 | Which of the following best describes the pharmacotherapeutic meeting with GPs?

A regular meeting without concrete agreements	14 (17.9%)
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A regular meeting with concrete agreements	33 (42.3%)
A regular meeting with assessment of agreements	31 (39.7%)
<hr/>	
17 Which of the following best describes the pharmacy?	
Inside a health centre (GP, pharmacy and other healthcare providers)	32 (41.0%)
A pharmacy and GP practice under one roof	8 (10.3%)
A pharmacy and GP practice in different locations	38 (48.7%)
<hr/>	
18 Kind of pharmacy	
Chain pharmacy	16 (20.5%)
Independent pharmacy (including franchising formula)	62 (79.5%)
<hr/>	
19 Location of the pharmacy	
In a town \geq 100,000 inhabitants	21 (26.9%)
In a town \leq 100,000 inhabitants	23 (29.5%)
In a rural area	34 (43.6%)
<hr/>	
20 Do you have a consultation room at your disposal?	
Yes	78 (100%)
<hr/>	
Pharmacist characteristics	
<hr/>	
21 Age	
<hr/>	
22 Gender	
<hr/>	

CHAPTER 4.3

Diagnosis of acute cystitis in primary care: Symptom-based versus urinalysis-based diagnosis

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Accepted for publication by

Primary Health Care Research and Development

Abstract

Aim

This study aimed to provide insight into the congruity of acute cystitis (AC) diagnosis in women, measured both by the Acute Cystitis Symptom Score (ACSS) questionnaire and urine test(s) with dipstick/dipslide.

Background

The ACSS questionnaire was developed as a self-administering tool for assessing urinary symptoms, quality of life (QoL) and treatment outcomes in healthy, nonpregnant female patients with AC.

Methods

This prospective observational cohort study compared AC diagnosis based on the questionnaire with a general practitioner (GP) diagnosis based on dipstick/dipslide test(s). Questionnaire form A (typical and differential symptoms, QoL and relevant conditions) was filled in by the patient group, women suspected for AC visiting a GP practice with a urine sample, and the reference group, women visiting a community pharmacy for any medication. Analyses were performed based on the assumption that the GP diagnosis with urine test(s) was correct. Divergent result(s) of urine test(s) and questionnaire were analysed for scores of all individual questionnaire domains. Statistical analyses included descriptive statistics and positive predictive value (PPV) and negative predictive value (NPV) of the questionnaire and urine test(s).

Findings

In the patient group, 59 women were included, 38 of whom a GP positively diagnosed for AC. The reference group included 70 women. The PPV of the questionnaire was 77.3%, and the NPV was 73.3%. Analysis of patient data for divergent results showed that differential symptoms, QoL and relevant conditions explained false-positive and false-negative results. Revised results (most probable diagnosis) based on this analysis showed a PPV and NPV of 88.6% and 73.3% for the questionnaire and 100% and 76.2% for the urine test(s). For use in primary care, a reduction in false-positive and false-negative results can be achieved by including scores for differential symptoms, QoL and relevant conditions, alongside a total typical symptoms score of 6 or higher.

Introduction

In healthy, non-pregnant women, AC is one of the most frequent indications for antibiotic prescriptions in primary care [1-3]. A correct diagnosis is vital to minimise unnecessary antibiotic prescriptions since the overuse of antibiotics is recognised as the main driver of antimicrobial resistance [4]. Nevertheless, the undertreatment of an AC episode may negatively impact women's QoL [5-9].

The most reliable diagnosis is made by performing a urine culture, which is expensive and time-consuming and therefore less suitable for everyday practice. Alternatively, the nitrite dipstick test (fast but may give a false-negative result) [10], the urinary sediment (requires microscopy and a skilled investigator) and the dipslide (has a delay of 24 hours for the results) are most widely applied [11]. In the Netherlands, the GP guidelines recommend performing a dipstick test followed by a dipslide test or culture if necessary [12].

The high prevalence of recurring AC in women leads to frequent GP visits [13]. Shortages of healthcare providers [14] and diagnoses at out-of-hours primary care where antibiotics are prescribed without urine test(s) [15] urge considering efficient ways to deal with recurring AC. Many women may recognise an AC episode themselves, potentially based on previous experiences [16].

The Acute Cystitis Symptom Score (ACSS) questionnaire was developed as an instrument to support self-reported AC diagnosis in female patients [17]. The questionnaire assesses the severity of typical and differential symptoms and their impact on QoL in women with suspected AC to differentiate it from other urological disorders while signalling differential conditions and assessing patient-reported outcomes [17-24]. Previously, the questionnaire was clinically validated in patients with suspected AC in hospital settings [17, 25-27], whereas AC patients in the Netherlands turn to primary care for diagnosis and treatment.

This study aimed to provide insight into the congruity of AC diagnosis, measured by the ACSS questionnaire and urine test(s), after translation and linguistic assessment of the questionnaire in the Dutch language.

Materials and Methods

Study design

In this prospective observational cohort study, AC diagnosis based on the self-reporting ACSS questionnaire was compared to AC diagnosis based on urine test(s) because of AC symptoms [12]. According to the actual GP procedure, AC-positive patients were defined as patients with a positive dipstick or a positive dipslide, in the case of a negative dipstick (Figure 1). The study was performed between February 2020 and July 2021, with an interruption from mid-March until October 2021 because of the COVID-19 pandemic.

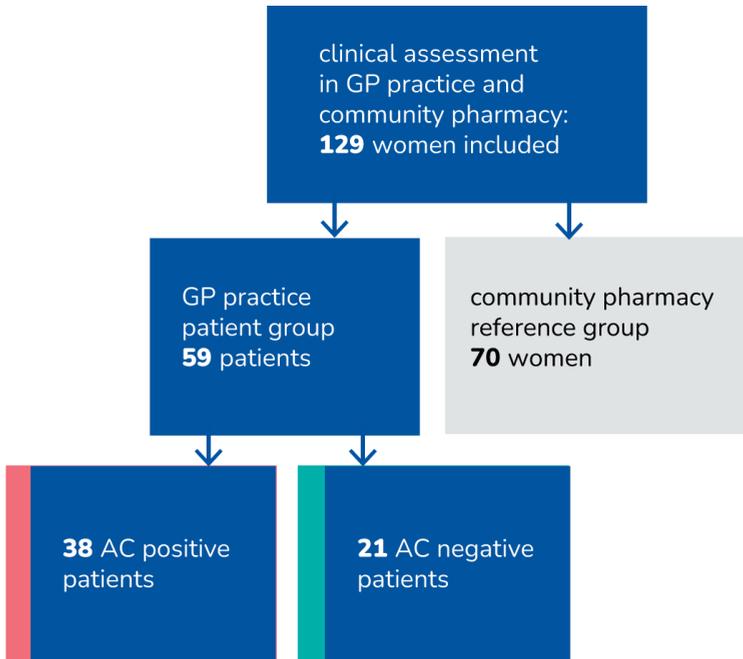
Settings and participants

The study was performed in two GP practices in different locations. In the first location, a community pharmacy and a GP practice (five part-time working GPs) were situated in a rural area, and they cooperated in a regional primary care network. In the second location, both the pharmacy and the GP practice (four GPs) were located in an urban health centre and closely collaborated. In both GP practices, the practice assistants were responsible for performing urine tests and preparation of antibiotic prescriptions. Antibiotic prescriptions were approved by the GP before transferring them to the community pharmacy.

Women who gave a urine sample because of AC symptoms received information about the study procedures and were invited to participate in the patient group.

Patient permission was solicited to obtain urine test result(s) from the GPs. Women visiting the GP practice were excluded from the patient group if (1) they were not fluent in Dutch, (2) had antimicrobial therapy within two weeks prior to the GP visit, (3) were pregnant, (4) used other drug therapy (such as NSAIDs) within 48 hours prior to the GP visit that might affect the severity of symptoms, (5) had recent bladder catheterisation or other invasive manipulations in the urinary tract or (6) had known anatomic or functional abnormality of the urinary tract. However, women who visited one of the community pharmacies for any prescription except an antibiotic and without suspected AC at the time of inclusion received information about study procedures and were invited to participate in the reference group (Figure 1).

Figure 1. Study design The Acute Cystitis Symptom Score questionnaire



Questionnaire validation studies and content

The ACSS questionnaire consists of forms A and B (Supplementary material). Form A is used at the start of symptoms and contains four domains: (1) the typical domain with six questions about AC symptoms, (2) the differential domain with four questions about differential symptoms, (3) the QoL domain with three questions and (4) the relevant condition domain with questions on menses, pregnancy, premenstrual syndrome (PMS), menopause and diabetes mellitus. Symptoms in the first two domains are scored from 0 (not present) to 3 (severe) to measure symptom severity. QoL items are scored from 0 (not affected) to 3 (extremely affected). Items of the relevant condition domain have binary yes/no answer options.

Follow-up form B is used to assess the therapy result [24]. Form B contains all form A domains and an additional domain on dynamics: change of symptoms approximately one week after the first GP visit, scored as 0 (feel back to normal with all symptoms gone), 1 (feel much better with most symptoms gone), 2 (feel somewhat better with most symptoms still present), 3 (feel

about the same with no changes in symptoms) and 4 (feel worse with a worsened condition). Previous validation studies have shown an optimal threshold for the total typical symptoms score of 6 for diagnosing AC [17, 25-27].

Translation, linguistic and cognitive assessment

The translation and linguistic assessment of the Dutch version of the ACSS questionnaire were performed per the Linguistic Validation Manual for Patient-Reported Outcomes (PRO) instrument guidelines [28]. Two independent translators produced primary, forward translations into the Dutch language from the validated Russian and American English ACSS versions, respectively [29]. These translations were discussed with three women who experienced AC in the past, a GP and a community pharmacist, leading to the first version, which was back-translated into English by an independent native speaker and compared with the original English version to detect relevant differences.

The resulting second version was used for cognitive assessment carried out with nine Dutch-speaking women who had varying educational levels and ages and did or did not experience AC in the past. The researchers discussed comments from these women with the developers of the original ACSS questionnaire. This discussion led to the final study version of the Dutch ACSS questionnaire (Appendix).

Data collection

Women in the patient group filled in the Dutch ACSS questionnaire form A manually, electronically or telephonically, identifying essential characteristics (e.g. age and educational level). Afterwards, the researcher made an appointment with the patient to fill in form B after finishing treatment telephonically. Only patients who filled in questionnaire form A within four days after visiting the GP practice were included. Notably, reference group women filled in form A with essential characteristics when visiting a community pharmacy.

Definition of outcomes: diagnosis

The GP practices performed a dipstick test for all patients suspected for AC, assessing the presence of nitrite and leukocytes (5-10 white blood cells per mL- WBC/ml) [10]. If nitrite was positive, an antibiotic was prescribed according to the urinary tract infections (UTI) guideline [12]; if nitrite was

negative and leukocytes were positive a dipslide was performed [12]. Moreover, according to the guideline, a dipslide was performed if leukocytes were negative, but AC was suspected based on patient complaints. An antibiotic was prescribed if the dipslide was positive (colony-forming units CFU $\geq 10^4$ /ml). AC-positive patients were defined as patients with one or more AC symptoms (dysuria, frequency, urgency or hematuria) and a positive dipstick or positive dipslide.

Data analysis

Descriptive statistics were used for demographic characteristics. Education levels were assigned according to the Statistic Netherlands database (CBS) [30]. Comparable to earlier validation studies, the reliability of the translated ACSS questionnaire was analysed by calculating Cronbach's α and Guttman split-half reliability for the total questionnaire and all individual domains. Cronbach's α was also calculated for the typical symptoms domain combined with the QoL domains, with only three items. Moreover, because of higher reliability, splitting into halves was performed depending on odd and even ordinary numbers of items. For the calculation of Cronbach's α , no missing values were allowed. Therefore, differential question 10a of the ACSS (measurement of body temperature) was marked as 'temperature < 37.5 °C if a woman had not measured her temperature but had answered question 10 with 'having no feeling of fever'.

The translated ACSS questionnaire was considered reliable if Cronbach's α and Guttman split-half reliability were higher than 0.80. For discriminative ability, receiver operating characteristics (ROC) analysis using a non-parametric test was performed on the total typical symptoms score for AC-positive patients as a stated variable to determine the best cut-off value. Typical symptom scores, differential symptom scores, QoL item scores and domain scores were compared for AC-positive patients and AC-negative patients, for AC-positive patients and reference group and for AC-negative and reference group, using Wilcoxon signed ranks test (significant if $p < 0.05$). These analyses were performed assuming that a GP diagnosis with urine test(s) was correct. Furthermore, a Mann-Whitney U test was performed to compare scores for individual questionnaire items for AC-positive patients, AC-negative patients and reference group women (significant if $p < 0.05$).

Moreover, a pairwise Wilcoxon signed rank test was performed to compare scores of AC-positive patients before and after antibiotic treatment (significant if $p < 0.05$).

The positive and negative results of the ACSS questionnaire based on the total typical symptoms score (≥ 6 or < 6) and the GP-guideline diagnosis based on the urine test(s) were compared. For patients with a divergent diagnosis for the ACSS questionnaire and GP practice with typical symptom scores, the scores for differential symptoms, QoL and additional data were mapped out and discussed with the research team GP to determine the most probable diagnosis. ROC analysis was also performed for the most probable diagnosis with AC-positive patients and controls plus AC-negative patients (stated variable) and the total typical symptoms score (tested variable). Moreover, typical symptom scores, differential symptom scores, QoL item scores and domain scores were compared for AC-positive patients and AC-negative patients, for AC-positive patients and reference group, and for AC-negative patients and reference group using Mann-Whitney U test (significant if $p < 0.05$). Data were analyzed using Statistical Package for Social Science (IBM SPSS) for Windows, version 27.0. Additionally, R v.3.5.2 with in-built and additional packages was used for comparative analyses and graphical representation of the results (R Core Team, 2017, Wickham H., 2017).

Results

Participants

In total, 64 patients completed the ACSS questionnaire. Five patients were excluded because questionnaire A was completed more than four days after the urine test(s) in GP practice. Of the remaining 59 patients, 38 were AC-positive patients, and 35 followed up on treatment results. The AC-negative patients were not treated and had no follow-up.

Table 1. Participants' characteristics. AC diagnosis according to GP-guideline

	Patient group (n = 59)		Reference group (n = 70)
	AC positive patients (n = 38)	AC negative patients (n = 21)	
Median age in years (min-max)	51.5 (19-80)	48.0 (27-75)	54.5 (19-79)
Education, percentage (number)			
Primary	34.2% (13)	33.3% (7)	30.0% (21)
Secondary	39.5% (15)	33.3% (7)	34.3% (24)
Higher	25.3% (10)	33.3% (7)	35.7% (25)

A total of 70 women were included in the reference group (Figure 1). No statistically significant differences were found between AC-positive patients and reference group women in age and educational level (Table 1). For all patients, the median number of days between the start of symptoms and a GP visit was 4.0 days (0–30) and 74.5% of all patients visited a GP practice within five days after symptoms started.

Reliability of the ACSS questionnaire

The Cronbach's α and Guttman split-half reliability for the total questionnaire, for the typical domain and the QoL plus typical domain were higher than 0.80 (Table 2). Cronbach's α for the differential domain containing severely divergent items was 0.49. ROC analysis performed for a GP diagnosis with AC-positive patients and reference group women plus AC-negative patients (stated variable) and the total typical symptoms score (tested variable) resulted in an area under the curve (AUC) of 0.93 (95%-CI, 0.89–0.98), with a sensitivity of 88.5% and specificity of 89.0% at a cut-off point of 6 for the summary score of the typical domain in the ACSS.

Table 2. Reliability analysis per domain for all included patients and controls

Domain	All respondents (n = 129)
Total questionnaire ^a	
Cronbach's alpha (95%-CI)	0.87 (0.84 - 0.90)
Guttman split half coefficient	0.85
Typical domain	
Cronbach's alpha (95%-CI)	0.82 (0.77 - 0.87)
Guttman split half coefficient	0.81
Differential domain	
Cronbach's alpha (95%-CI)	0.49 (0.33 – 0.62)
Quality of Life domain	
Cronbach's alpha (95%-CI)	0.87 (0.82 – 0.90)
Quality of Life + Typical domain	
Cronbach's alpha (95%-CI)	0.90 (0.87 – 0.92)
Guttman split half coefficient	0.83

^a Typical, differential and quality of life domains. As the items of the additional domain are dichotomous, they were not included in this analysis.

Scores for typical symptoms, differential symptoms and quality of life

Scores for frequent urination of small volumes, urgent urination, feeling pain or burning when passing urine, incomplete bladder emptying, total typical domain, vaginal discharge, general discomfort, and total QoL were significantly higher for AC-positive patients than AC-negative patients (Table 3).

Table 3. Comparison of typical symptom scores, differential symptom scores, QoL item scores and domain scores between: A) AC positive patients (n = 38) versus AC negative patients (n = 21); B) AC positive patients (n = 38) versus reference group (n = 70); C) AC negative patients (n = 21) versus reference group (n = 70). AC diagnosis according to GP-guideline; differences statistically significant if p < 0.05

Compared groups		p-values (significant p < 0.05)		
		A	B	C
Typical domain	Frequency	0.013	<0.001	<0.001
	Urgency	0.037	<0.001	<0.001
	Painful urination (dysuria)	0.009	<0.001	<0.001
	Incomplete bladder emptying	0.021	<0.001	<0.001
	Suprapubic pain	0.592	<0.001	<0.001
	Visible blood in urine	0.925	<0.001	<0.001
Differential domain	Flank pain	0.570	<0.001	<0.001
	Vaginal discharge	0.006	0.090	<0.001
	Urethral discharge	0.372	0.193	0.027
	High body temperature, fever	0.403	0.016	0.378
Quality of life (QoL) domain	General discomfort	0.020	<0.001	<0.001
	Everyday activities/ work	0.059	<0.001	<0.001
	Social activities	0.328	<0.001	0.005
Domains	Typical	0.003	<0.001	<0.001
	Differential	0.151	<0.001	<0.001
	QoL	0.031	<0.001	<0.001
	Typical plus QoL	0.002	<0.001	<0.001

The median (mean) typical symptom scores for frequency were 2.0 (2.13), 1.5 (1.43) and 1.0 (0.5) for AC-positive, AC-negative and reference group women, respectively (Figure 2A). Summary scores of the domains (Typical, Differential, QoL) for AC-positive patients versus reference group and AC-negative patients versus reference group differed significantly (Table 3, Figure 2B).

The percentages of AC-positive patients and reference group women that experienced frequent urination were 100% and 37.1%. Of the AC-positive patients, 100% scored mild, moderate or severe for frequency (5–6 times or

more daily), whereas this percentage was 37% for the reference group women (Figure 3): 24% scored mild and 13% scored moderate for frequency.

Figure 2. Boxplots with A) typical symptom scores (median, IQR) and B) ACSS domains scores (median, IQR), both for AC positive patients (n=38), AC negative patients (n=21) and reference group (n=70), based on GP-guideline diagnosis

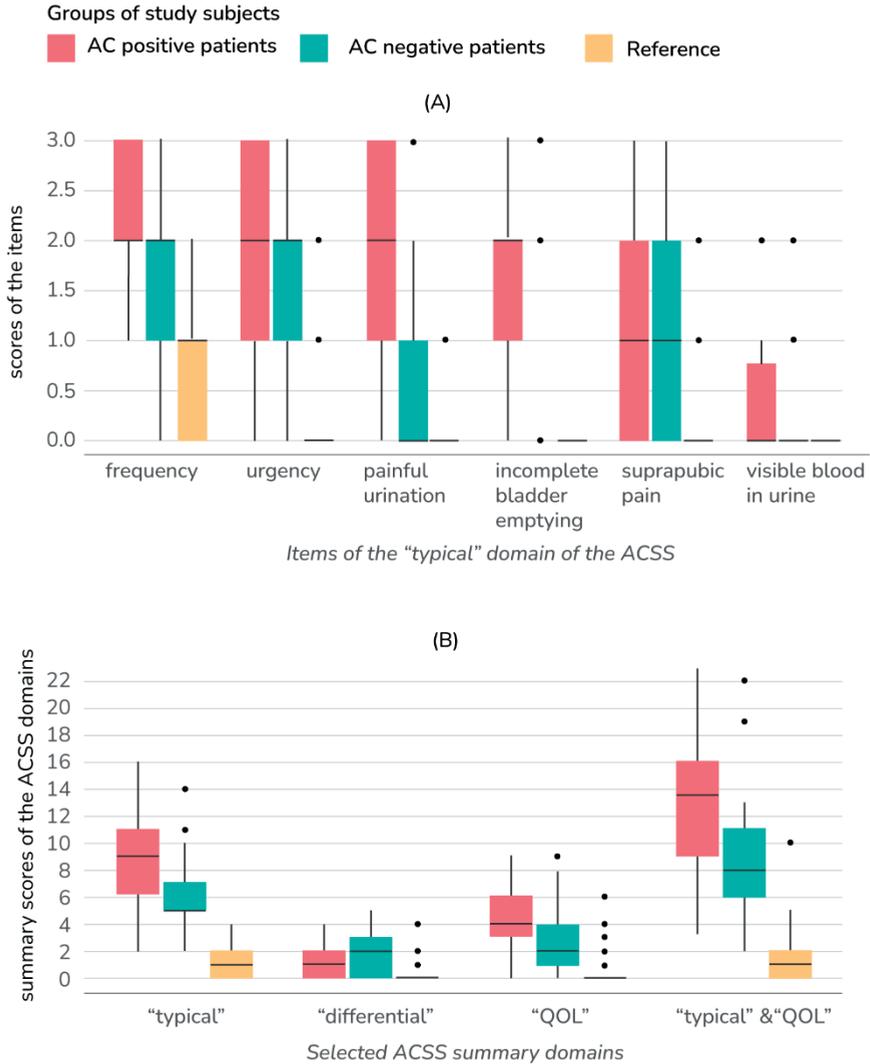
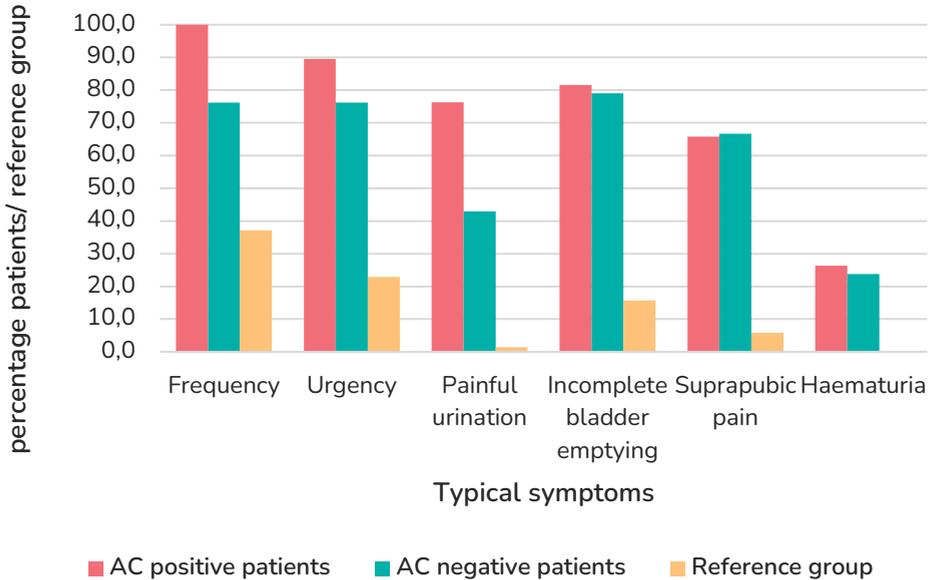


Figure 3. Percentages of AC positive patients (n=38), AC negative patients (n=21) and reference group (n=70) for typical symptoms with score ≥ 1 (mild, moderate or severe symptoms). based on GP-guideline diagnosis



Vaginal and urethral discharge scores did not differ significantly for AC-positive patients and reference group women contrary to scores for individual typical domain symptoms, remaining differential symptoms, QoL domain items and total symptom scores for all domains, which were significantly higher for AC-positive patients than for reference group women ($p < 0.05$) (Table 3). Moreover, the median (mean) typical symptom score for blood in the urine was lowest at 0.00 (0.32) for AC-positive patients and comparable to scores for blood in the urine for AC-negative patients. For AC-positive patients, mean QoL scores were 2.00 for general discomfort, 1.53 for influence on work/daily activities and 0.79 for influence on social activities.

Comparison of ACSS questionnaire result and GP diagnosis

In the GP practices, 38 patients were diagnosed as AC-positive and 21 as AC-negative. Based on the total typical symptoms score ≥ 6 , the ACSS questionnaire diagnosed 44 patients as AC-positive and 15 as AC-negative. The PPV of the ACSS questionnaire (total typical symptoms score ≥ 6) was 77.3%, whereas the NPV was 73.3%.

Analysis of divergent diagnoses

Based on an ACSS questionnaire score <6, four patients did not have AC, while the urine test(s) showed a positive result (Table 4A). In three cases, the patient probably rated the symptom severity too low. When filling in the questionnaire, one patient reported she always recognised having an AC episode by urine scent and goosebumps when urinating.

The conclusion was that the ACSS questionnaire probably was false-negative for AC for these four cases.

The ACSS questionnaire diagnosed ten patients as AC-positive, while the urine test(s) showed a negative result.

In five cases, differential diagnostics were probably indicated because of differential symptoms and blood loss that worried the patient. In one patient, the GP had already started differential diagnostics.

The conclusion was that the ACSS questionnaire probably was false-positive for AC (Table 4B).

The other five patients had evident AC symptoms, but in four, the urine test(s) most probably was negative because of a short duration of stay of urine in the bladder. The fifth patient forgot nitrofurantoin prophylaxis after sexual intercourse but ingested 200 mg of nitrofurantoin before visiting a GP. In another patient, the symptoms subsided after using an extended prescription of fosfomycin from an earlier AC episode, which she had at home. Despite negative urine test(s), the GP prescribed one patient nitrofurantoin because of symptoms. The conclusion was that the GP practice diagnosis probably was false-negative for AC (Table 4C).

Table 4A. Patients with negative ACSS questionnaire result and positive urinary test(s) result but most probable diagnosis AC positive (false negative ACSS)

Patient number	3	16	41	43
Age (yrs)	70	23	47	63
ACSS form A result ^a	0	0	0	0
Total score typical symptoms ^{b, f}	4	5	3	2
Total score differential symptoms ^{d, f}	0	2	2	1
Total score QoL ^{e, f}	5	1	3	1
ACSS form B result ^g	0	1	2	1
Urinary test(s) result ^h	1	1	1	1
most probable diagnosis ^k	1	1	1	1
Argumentation for ACSS false negative	Clear growth dipslide (10 [^] 7), scores QoL discomfort and daily activities moderate; probably symptoms rated too low	Moderate scores for frequency, abdominal pain, flank pain, mild for incomplete emptying of the bladder; probably symptoms rated too low.	Clear growth dipslide (10 [^] 5), ACSS form B: most symptoms still present; probably symptoms rated too low	Patient recognizes AUC by urine scent and goosebumps from bladder to head when urinating

Table 4B. Patients with positive ACSS questionnaire result and negative urinary test(s) result but most probable diagnosis AC negative (false positive ACSS)

Patient number	4	6	14	21	45
Age (yrs)	27	62	49	29	60
ACSS form A result ^a	1	1	1	1	1
Total score typical symptoms ^{b, f}	6	8	7	10	7
Total score differential symptoms ^{d, f}	2	6	3	3	0
Total score QoL ^{e, f}	2	1	3	9	2
ACSS form B result ^g	2	2	1	-	1
Urinary test(s) result ^h	0	0	0	0	0
most probable diagnosis ^k	0	0	0	0	0
Arguments for false positive ACSS	GP started differential diagnostics because of patient complaining of irritable bowel, vaginal discharge, obstipation	Form A: moderate scores for flank pain/ vaginal discharge/ fever; Form B: majority of symptoms still present; postmenopausal; possibly vaginal atrophy; differential diagnostics indicated	Forms A and B: mild vaginal/ urethral discharge; score QoL discomfort severe; Form B: majority of typical symptoms gone away; possibly vaginal bacteriosis; differential diagnostics indicated	Severe complaints for frequency, urgency, abdominal pain and flank pain which could indicate a higher UTI, but a positive urine test would be expected. Differential diagnostics indicated.	Moderate scores for frequency, urgency, blood in urine (patient was very worried), mild score for burning pain when urinating; possibly vaginal atrophy; differential diagnostics indicated.

Table 4C. Patients with positive ACSS questionnaire result and negative urinary test(s) result but most probable diagnosis AC positive (false negative result for GP)

Patient number	2	11	25	33	48
Age (yrs)	39	53	49	48	73
ACSS form A result ^a	1	1	1	1	1
Total score typical symptoms ^{b, f}	10	11	7	14	7
Total score differential symptoms ^{d, f}	3	1	1	0	0
Total score QoL ^{e, f}	1	2	1	8	4
ACSS form B result ^g	1	1	0	0	0
Urinary test(s) result ^h	0	0	0	0	0
most probable diagnosis ^k	1	1	1	1	1
Arguments for most probable diagnosis	Evident AUC symptoms; symptoms disappeared by natural course; no vaginal and urethral discharge in ACSS B; urinetest negative, possibly by short urine duration of stay in bladder.	Evident AUC symptoms, score QoL discomfort moderate; patient used delayed prescription fosfomycin (from earlier AUC) after negative urine test, frequency and burning pain disappeared; possibly short urine duration of stay in bladder.	Evident AUC symptoms; symptoms disappeared by natural course; urine test negative possibly by short duration of stay in bladder.	Evident AUC symptoms, scores QoL discomfort and work severe; patient forgot prophylaxis after sexual intercourse but ingested 200 mg nitrofurantoin before visiting the GP.	Evident AUC symptoms; moderate scores for QoL discomfort and daily activities; GP prescribed antibiotic based on symptoms, urine test negative possibly by short duration of stay in bladder.

^a Result ACSS questionnaire based on total typical symptoms score ≥ 6 : 1 = AC positive; 0 = AC negative

^b Total typical symptoms score: frequency + urgency + burning pain when urinating + incomplete emptying of the bladder + abdominal pain + blood seen in urine

^d Total differential symptoms score: loin pain + vaginal discharge + urethral discharge + high body temperature + temperature specified

^e Total QoL score: general discomfort + influence on work/ daily activities + influence on social activities

^f severity score per symptom/ item: 0 = absent, 1 = mild, 2 = moderate, 3 = severe

^g ACSS B: treatment result: 0 = all symptoms have gone away; 1 = majority of symptoms have gone away; 2 = majority of symptoms is still present; 3 = no changes in my symptoms; 4 = my condition is worse^h Urinary test result: dipstick and eventual dipslide: 1 = AC positive; 0 = AC negative

^k most probable diagnosis, based on evaluation with independent GP: 1 = AC positive; 0 = AC negative

Revision of PPV, NPV and ROC based on analysis of divergent results

The PPV and NPV were recalculated for the ACSS questionnaire and GP diagnosis based on the most probable diagnoses. Figures 4A and 4B show the boxplots for the typical symptoms and the domains for AC-positive and AC-negative patients and the reference group based on the most probable AC diagnoses. The ACSS questionnaire resulted in a PPV of 88.6% and an NPV of 73.3%, while the revised GP diagnosis resulted in a PPV of 100% and an NPV of 76.2%. Moreover, ROC analysis for most probable diagnosis with AC-positive patients and reference group women plus AC-negative patients (stated variable) and the total typical symptoms score (tested variable) resulted in an AUC of 0.97 (95%-CI, 0.94–0.99) with a sensitivity of 90.7% and specificity of 94.2% at a cut-off point of 6. Figure 4 shows typical symptom scores and ACSS domain scores for AC positive patients, AC negative patients and reference group based on most probable diagnosis. Figure 5 shows that the total typical symptoms score for the most probable diagnosis has a clearer distinction between AC-positive and AC-negative patients in comparison to the summary scores achieved by using the GP-guideline approach.

Figure 4. Boxplots with A) typical symptom scores (median, IQR) and B) ACSS domain scores (median, IQR), both for AC positive patients (n = 43), AC negative patients (n = 16) and reference group (n = 70), based on most probable diagnosis, after evaluation of divergent results of ACSS questionnaire and urine test(s)

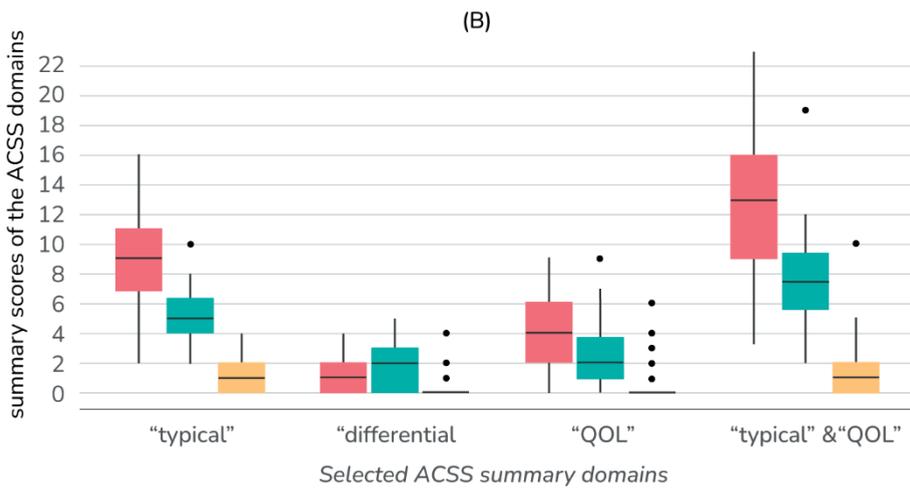
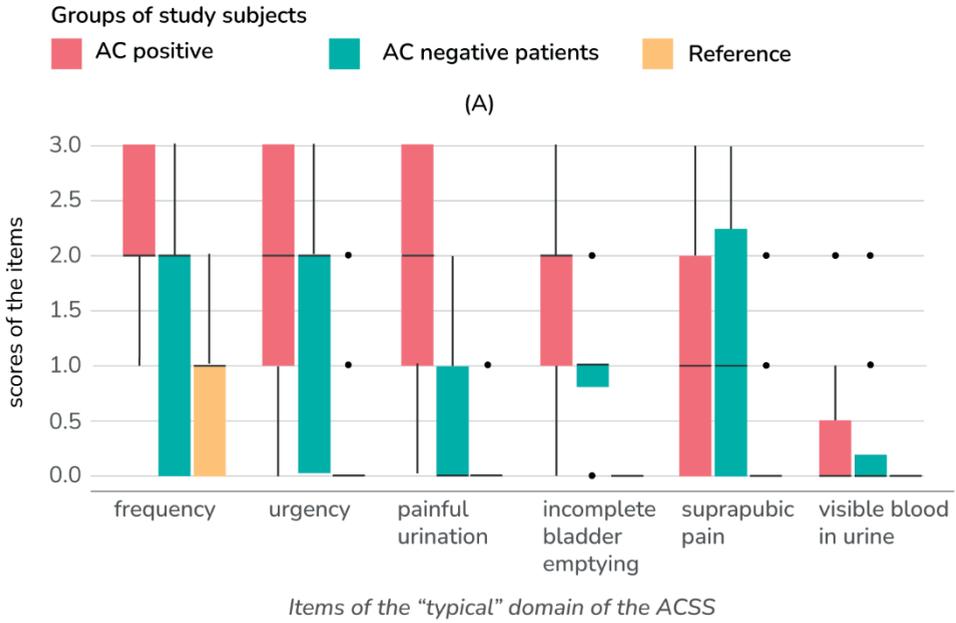
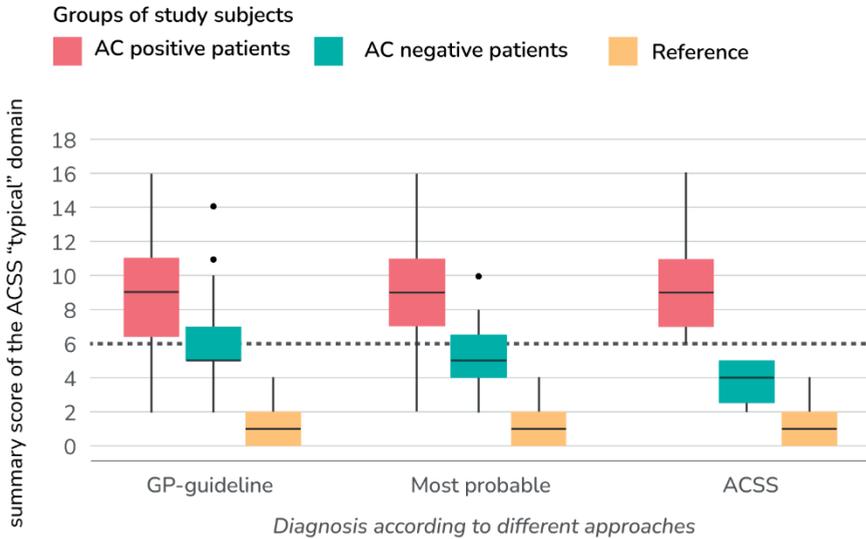


Figure 5. Boxplot with total typical symptom scores (median, IQR) for AC positive patients (n = 38), AC negative patients (n = 21) and reference group (n = 70), (a) based on GP-guideline diagnosis, (b) based on most probable diagnosis after evaluation of divergent results of ACSS questionnaire and urine test(s), and (c) based on ACSS diagnosis (summary score ≥ 6)



Comparison of domain scores ACSS forms A and B

For 35 of 38 (92%) patients who received antibiotic treatment after being diagnosed as AC-positive at a GP practice, ACSS questionnaire form B was available. The median interval between filling in questionnaire forms A and B was ten days (6–35). A comparison of symptom and item scores of the typical, differential and QoL domains for AC-positive patients before and after antibiotic treatment showed significantly lower scores after treatment ($p < 0.05$) than at the start of treatment for all symptoms and items, except abnormal vaginal and urethral discharge and specified body temperature, with the caveat that only three patients had taken their temperature. When filling in questionnaire form B, 54.3% ($n = 19$) of the AC-positive patients who received antibiotic treatment felt back to normal, while 29.0% ($n = 11$) felt much better.

Discussion

The reliability, sensitivity and specificity of the Dutch translation of the ACSS questionnaire were comparable to results of earlier ACSS validation studies. However, assuming that GP urine test result(s) were correct, the PPV and NPV for the questionnaire were approximately 25% lower than those for the urine test(s). Divergent results for the ACSS questionnaire and urine test(s) probably were caused by [1] patients (ACSS symptom score < 6), rating symptom severity too low or recognising an AC episode by urine scent (false-negative ACSS), [2] symptoms caused by a differential condition or a high score on blood in the urine (false-positive ACSS) and [3] the short duration of stay of urine in the bladder (false-negative GP diagnosis).

The Dutch translation of the ACSS questionnaire showed a sensitivity of 88.5% and specificity of 89.0% based on a correct GP guideline diagnosis, which increased to 90.7% for sensitivity and 94.2% for specificity based on a revised, most probable diagnosis at the cut-off point of ≥ 6 for the total typical symptoms score, which complies with earlier ACSS validation studies (17, 26, 27).

For practical use in primary care, a reduction in false-positive and false-negative results was possible, achieved by including scores for differential symptoms, QoL scores, relevant conditions and moderate or severe scores for blood in the urine in the evaluation of the questionnaire with a total typical symptom score of ≥ 6 .

A false-negative ACSS may result from patients rating symptoms too low, possibly because the questionnaire could not be filled in when handing in the urine at a GP practice. Moreover, when filling in the questionnaire up to 4 days after the GP visit, some patients may have struggled to recall the severity of earlier symptoms. Furthermore, older women may be less sensitive to typical symptoms, and UTIs may present differently in them (16, 31).

The inclusion of differential symptoms and the QoL in evaluating questionnaire results may decrease false-negative results.

A false-positive ACSS may result from typical symptoms caused by other conditions. The genitourinary syndrome of menopause includes vulvovaginal atrophy and postmenopausal modifications of the lower urinary tract (32).

Blood in the urine is a typical AC symptom, but gross haematuria may also be caused by postmenopausal vaginal atrophy or an underlying malignancy (over 10% of patients) (33). Smoking is associated with 25% of bladder cancers in women and patients over 35 years of age, and patients with more than a 10-pack-year smoking history have an increased risk of malignancy (33). This study advises that patients with AC symptoms and gross haematuria should be referred for urologic evaluation.

In postmenopausal women, uterine prolapse may lead to voiding dysfunction symptoms such as frequent urination of small volumes and the sensation of incomplete bladder emptying after urination (34), possibly adding to false-positive results of typical symptoms. Typical symptoms may also result from an overactive bladder (OAB). However, UTI symptoms are generally acute, whereas OAB symptoms are generally chronic (35). Differential symptoms such as vaginal or urethral discharge with typical symptoms including dysuria and abdominal pain may be caused by sexually transmitted diseases such as Chlamydia. These differential symptoms also may indicate a false-positive result of the questionnaire.

Loin pain score, mostly combined with fever, may point to tissue invasion and pyelonephritis (36). The European Association of Urology (EAU) guideline advises performing urine culture and antimicrobial susceptibility testing in patients with pyelonephritis (37). Moreover, adding smoking to relevant conditions and including differential symptoms, QoL and relevant conditions in evaluating questionnaire results may decrease false-positive results. A false-negative GP diagnosis by a urine test(s) may occur when the duration of stay of urine in the bladder is too short (10), possibly because postmenopausal periods are associated with increased nocturia (38). Clinically relevant nocturia (≥ 2 voids per night) affects 2%–18% of women 20 to 40 years, rising to 28%–62% for those 70–80 years (39). Nevertheless, AC also increases the frequency of urinating, possibly leading to nightly urinating. Most GP practices ask for morning urine but do not automatically inform patients about sufficient length of urine stay in the bladder. Moreover, studies have found that women with typical complaints and a negative culture may still have an *E. coli* infection (40–42). However, our study design did not allow us to detect this combination as a cause for false-negative results for urine testing in a GP practice. Also, a nitrite positive dipstick is only found in the presence of Gram-negative

uropathogens and not in the presence of enterococci, which can cause acute cystitis in a lower number of patients. Using an ACSS questionnaire with a cut-off score of 6 or higher, thus might actually decrease false-negative results in GP practice.

Compared with AC-positive patients, reference group women scored high for mild and moderate urinary frequency. During the cognitive assessment of the questionnaire, the number of urinating moments was deemed low compared to the corresponding scores. Thus, increasing the number of urinating moments for mild, moderate and severe frequency may increase the distinctiveness of this typical symptom.

The EAU guideline on urological infections (43) considers the evidence for AC diagnosis in women as strong when it is based on a focused history of dysuria, frequency and urgency and absence of vaginal discharge or irritation. In this study, mean differential symptom scores of AC positive patients for vaginal discharge were low (0.18), with scores between 0 and 2. Vaginal discharge in AC-positive patients did not differ significantly from the reference group, aligned with an earlier study that showed that complaints of abnormal vaginal discharge were found not to decrease AC probability (21). Thus, the absence of vaginal discharge in the EAU guideline might be re-evaluated.

The added value of the ACSS questionnaire in Dutch clinical practice compared to urine testing is that the ACSS questionnaire can be filled in easily and fast by most women and can save contact time in primary care. The questionnaire provides information on seriousness of symptoms, on differential symptoms and influence on quality of life irrespective of the time of day women hand in urine. Moreover, relevant co-morbidities are asked out. Thus, it may also improve AC diagnosis in out-of-hours primary care (15). This may also be the case in other countries, as in some Canadian provinces (44, 45), New Zealand (46), and Queensland (Australia) (47, 48) women with recurring UTI can consult a trained pharmacist to receive an antibiotic without a preceding physician prescription. For AC diagnosing, these pharmacists use a simple questionnaire, a urine dipstick test or a guideline for acute cystitis diagnosing. Therefore, the ACSS questionnaire may improve diagnosis of acute cystitis by community pharmacists as well.

Strengths and Weaknesses

Because of the COVID-19 pandemic, the study was interrupted but resumed after six months. Based on earlier ACSS validation studies, in the design of the study we planned to include 50 women with suspected AC from 3 different GP practices and an equal number of women in the reference group to be able to validate the questionnaire (26,27). However, after including 9 patients in the first GP practice and 20 women in the reference group in the first pharmacy COVID-19 forced us to interrupt the study. In the second pharmacy we included 50 women for the reference group over a short period and decided to include 50 patients for the patient group in the second GP practice. The characteristics of the women included at the first location were comparable to those at the second location.

A strength was that the study was performed in as well an urban as a rural setting. A weakness was that the inclusion procedure in the second GP practice had to be adapted because of the pandemic. In the first location, patients were asked in person to enroll in the study and patients filled in questionnaire A immediately after handing in their urine sample. However, in the second location, patients handed in their urine at an unattended counter where they could find information about the study and filled in a consent form with permission to be telephoned by the researcher. The researcher allowed these patients to answer the ACSS questionnaire form A, form B and the identifying characteristics telephonically. Thereby, patients at the second GP practice filled in the questionnaire up to four days after handing in the urine sample, mostly after the start of antibiotic treatment. On this account, the patient was asked about the severity of symptoms at the time of handing in their urine sample. The adapted procedure impeded the inclusion of patients and made it impossible to calculate the patient response rate. Since only patients fluent in Dutch could be included, patients with low health literacy are missing and thus our results may not be representative for this patient group. Primary, secondary and higher education levels for the patient group with 33%, 37% and 30% respectively, are largely similar with national data for women 15-75 years in 2020 which were 26%, 38% and 34% respectively (49). Thus, the overall education level of the patient group was in the range of the overall national education level.

This study was performed during the COVID-19 epidemic. The mean score for influence on QoL social activities was 55% lower than reported in an earlier study (24), probably because social activities were minimal or not possible during lockdown periods. Moreover, all patients with a divergent result for the ACSS questionnaire and urine test(s) were included in the GP practice at the second location. The differences between the results of the questionnaire and urine test(s) may have been caused by the time interval between the GP practice visit and filling in the questionnaire. Because patient numbers in the first GP practice were much smaller than in the second GP practice, low statistical power prohibited statistical analysis of these differences.

Summary and Conclusion

Although the reliability of the ACSS questionnaire to establish AC was comparable to earlier studies for use in primary care, a reduction in false-positive and false-negative results was possible, achieved by including scores for differential symptoms, QoL, relevant conditions and moderate or severe scores for blood in the urine with a typical symptom score of 6 or higher.

4.3

Acknowledgements

The authors thank the copyright holders of the ACSS questionnaire, Prof Dr F Wagenlehner, Dr Jakhongir Alidjanov, Prof Dr Adrian Pilatz, Prof Dr Kurt Naber and Ozoda Alidjanova MD, for permitting us to translate the questionnaire into Dutch, using it for this study. We thank Prof. Dr. Adrian Pilatz and Prof. Dr. Florian Wagenlehner for reviewing the manuscript. We also thank GP practices Stevenshof and Glazen Linde, particularly practice manager Fleur Godijn and GP Marieke Stens MD, and community pharmacies Stevenshof and West-Friesland, particularly community pharmacists Henk-Frans Kwint PharmD PhD and Elze Alons PharmD for supporting the research in practice. Moreover, we thank Devika Rana and Valerie Kleuver for their work on this study in the context of their master's research, and the pharmacists and GPs who participated in the translation, linguistic and cognitive assessment process, particularly Rob Moss PharmD, Bart Knottnerus MD PhD GP, Karen de Leest PharmD and Bart Kremers PharmD. Finally, we thank the women who

participated in the translation and cognitive assessment process or participated in the study in GP and pharmacy practices.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of interest

None, Dr. Kurt Naber and Dr Jakhongir Alidjanov are copyright holders of the ACSS

Ethical standards

This study was submitted to the Medical Ethical Review Board of Utrecht Academic Hospital, which confirmed that no ethical approval was required as the study was not subject to the Medical Research Involving the Human Subjects Act (WMO) (19-701/C). The study was approved by the Institutional Review Board of the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University (UPF1908). Written informed consent was obtained from all women that were willing to participate and a three digit code was assessed to them that was used for the analysis of data.

Author's contribution

RL wrote the concept/protocol of the study, analysed the data and wrote the original draft. She implemented the contribution of co-authors and external reviewers up to final publication. During the process, she implemented input and feedback from her supervisors.

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Supplementary materials

Supplement 1: ACSS symptom score questionnaire Form A

Vragenlijst blaasontsteking		Eerste bezoek - Deel A				
		Vragenlijst ingevuld (Datum):				
		(dd / mm / jiji)				
Wilt u aankruisen of u in de afgelopen 24 uur last hebt gehad van een of meer van de volgende klachten en hoe erg de klachten waren						
Gebruikelijke klachten	1 Vaak plassen van kleine hoeveelheden urine (vaak naar de wc)	Geen last (0) <input type="checkbox"/>	Een beetje (1) <input type="checkbox"/>	Tamelijk erg (2) <input type="checkbox"/>	Heel erg (3) <input type="checkbox"/>	
		4x of minder per dag	5-6x per dag	7-8x per dag	9x of meer per dag	
	2 Plotselinge, sterke aandrang om te plassen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	3 Voelt u branderige pijn als u plast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	4 Gevoel dat u na het plassen weer zou moeten plassen (gevoel dat de blaas niet helemaal leeg is na het plassen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	5 Pijn in de onderbuik (lager dan uw navel), ook als u niet plast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6 Bloed in de urine gezien? (geen menstruatiebloed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>totaalscore van gebruikelijke klachten:</i> _____						
Andere klachten	7 Pijn in een of beide flanken (pijn in een of beide zijkanen van onderrug)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	8 Meer of andere vaginale afscheiding dan gewoonlijk (hoeveelheid, kleur en/of geur)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	9 Afscheiding uit de plasopening zonder dat u plast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	10 Gevoel dat u koorts of verhoging heeft?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	10a Als u uw temperatuur gemeten heeft, wilt u dan aankruisen hoe hoog die was <input type="checkbox"/> Ja <input type="checkbox"/> Nee	≤37,5 °C	37,6-37,9 °C	38,0-38,9 °C	≥39,0 °C	
<i>totaalscore van andere klachten:</i> _____						
11 Wilt u aankruisen hoeveel ongemak u de afgelopen 24 uur hebt gehad van uw klachten (kies het antwoord dat het dichtst bij komt)						
Kwaliteit van leven	0 Geen ongemak (helemaal geen klachten, ik voel me net zo als ik me gewoonlijk voel)					
	1 Een beetje ongemak (ik voel me een beetje slechter dan gewoonlijk)					
	2 Tamelijk veel ongemak (ik voel me behoorlijk slecht)					
	3 Heel veel ongemak (ik voel me vreselijk slecht)					
	12 Wilt u aankruisen hoe erg de klachten de afgelopen 24 uur uw dagelijkse activiteiten/werk hebben beïnvloed					
	0 Geen invloed (heb zoals gewoonlijk mijn dagelijkse activiteiten/werk kunnen uitvoeren of had niets gepland)					
	1 Een beetje invloed (heb mijn dagelijkse activiteiten/werk met enig ongemak kunnen uitvoeren)					
	2 Tamelijk veel invloed (heb mijn dagelijkse activiteiten/werk met moeite kunnen uitvoeren)					
	3 Heel veel invloed (bijna onmogelijk om mijn dagelijkse activiteiten/werk uit te voeren)					
	13 Wilt u aankruisen hoe erg de klachten de afgelopen 24 uur uw sociale activiteiten (vrienden ontmoeten, uitgaan...) hebben beïnvloed					
	0 Geen invloed (heb alles kunnen doen wat ik van plan was of was niets van plan)					
	1 Een beetje invloed (heb minder kunnen doen dan ik van plan was)					
2 Tamelijk veel invloed (heb veel minder kunnen doen dan ik van plan was)						
3 Heel veel invloed (door de klachten heb ik niets kunnen doen van wat ik van plan was)						
<i>totaalscore van kwaliteit van leven:</i> _____						
14 Wilt u aankruisen of het volgende wel of niet op u van toepassing is						
Aanvullende vragen	Menstrueert u (heeft u maandelijkse bloedingen)?				<input type="checkbox"/> Ja <input type="checkbox"/> Nee	
	Heeft u klachten zoals buikpijn in de week voor de menstruatie (Premenstruele klachten= PMS)?	Ja			Nee	
	Heeft u last van overgangsklachten (zoals opvliegers)?	Ja			Nee	
	Bent u zwanger?	Ja			Nee	
	Heeft uw arts vastgesteld dat u diabetes mellitus heeft (suikerziekte)	Ja			Nee	

Supplement 2: ACSS symptom score questionnaire Form B

Vragenlijst blaasontsteking Vervolgbezoek - Deel B

Vragenlijst ingevuld (Datum): (dd / mm / jiii)

Wilt u aankruisen of uw klachten (symptomen) veranderd zijn sinds het invullen van de eerste vragenlijst (kies het antwoord dat het beste weergeeft hoe u zich voelt)

Dynamiek

0 Ja, ik voel me zoals gewoonlijk, alle klachten zijn verdwenen
 1 Ja, ik voel me veel beter, de meeste klachten zijn verdwenen,
 2 Ja, ik voel me een beetje beter, een paar klachten zijn minder geworden of verdwenen
 3 Nee, ik voel me slechter, mijn klachten zijn erger geworden

Wilt u aankruisen of u in de afgelopen 24 uur last hebt gehad van een of meer van de volgende klachten en hoe erg de klachten waren

	Geen last (0)	Een beetje (1)	Tamelijk erg (2)	Heel erg (3)	
Gebruikelijke klachten	1 Vaak plassen van kleine hoeveelheden urine (vaker naar de wc)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	2 Plotselinge, sterke aandrang om te plassen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	3 Voelt u branderige pijn als u plast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	4 Gevoel dat u na het plassen weer zou moeten plassen (gevoel dat de blaas niet helemaal leeg is na het plassen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	5 Pijn in de onderbuik (lager dan uw navel), ook als u niet plast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	6 Bloed in de urine gezien? (geen menstratiebloed)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Totaalscore van gebruikelijke klachten:</i> _____					
Andere klachten	7 Pijn in een of beide flanken (pijn in een of beide zijkten van onderrug)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	8 Meer of andere vaginale afscheiding dan gewoonlijk (hoeveelheid, kleur en/of geur)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	9 Afscheiding uit de plasopening zonder dat u plast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	10 Gevoel dat u koorts of verhoging heeft?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	10a Als u uw temperatuur gemeten heeft, wilt u dan aankruisen hoe hoog die was	<input type="checkbox"/> Ja	<input type="checkbox"/> Nee	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	<i>totaalscore van andere klachten:</i> _____				
Kwaliteit van leven	11 Wilt u aankruisen hoeveel ongemak u de afgelopen 24 uur hebt gehad van uw klachten (kies het antwoord dat het dichtst bij komt)				
	0 Geen ongemak (helemaal geen klachten, ik voel me net zo als ik me gewoonlijk voel)				
	1 Een beetje ongemak (ik voel me een beetje slechter dan gewoonlijk)				
	2 Tamelijk veel ongemak (ik voel me behoorlijk slecht)				
	3 Heel veel ongemak (ik voel me vreselijk slecht)				
	12 Wilt u aankruisen hoe erg de klachten de afgelopen 24 uur uw dagelijkse activiteiten/werk hebben beïnvloed				
	0 Geen invloed (heb zoals gewoonlijk mijn dagelijkse activiteiten/werk kunnen uitvoeren of had niets gepland)				
	1 Een beetje invloed (heb mijn dagelijkse activiteiten/werk met enig ongemak kunnen uitvoeren)				
	2 Tamelijk veel invloed (heb mijn dagelijkse activiteiten/werk met moeite kunnen uitvoeren)				
	3 Heel veel invloed (bijna onmogelijk om mijn dagelijkse activiteiten/werk uit te voeren)				
	13 Wilt u aankruisen hoe erg de klachten de afgelopen 24 uur uw sociale activiteiten (vrienden ontmoeten, uitgaan...) hebben beïnvloed				
	0 Geen invloed (heb alles kunnen doen wat ik van plan was of was niets van plan)				
	1 Een beetje invloed (heb minder kunnen doen dan ik van plan was)				
2 Tamelijk veel invloed (heb veel minder kunnen doen dan ik van plan was)					
3 Heel veel invloed (door de klachten heb ik niets kunnen doen van wat ik van plan was)					
<i>totaalscore van kwaliteit van leven:</i> _____					
14 Wilt u aankruisen of het volgende wel of niet op u van toepassing is					
Aanvullende vragen	Menstrueert u (heeft u maandelijkse bloedingen)?		Ja	Nee	
	Heeft u klachten zoals buikpijn in de week voor de menstruatie (Premenstruele klachten= PMS)?		Ja	Nee	
	Heeft u last van overgangsklachten (zoals opvliegers)?		Ja	Nee	
	Bent u zwanger?		Ja	Nee	
	Heeft uw arts vastgesteld dat u diabetes mellitus heeft (suikerziekte)		Ja	Nee	

Supplement 3: CRF form

Identificatie van de Patiënt

Datum van onderzoek (dag/maand/jaar): _____ / _____ / _____

PatientCode-Nr: _____ P(atient)* C(ontrolle)**

Patient – vrouw met blaasontsteking en **Controle – patient zonder blaasontsteking ten tijde van onderzoek

Informatie van de vrouw

Vrouwen met of zonder blaasontsteking:

Leeftijd: _____ jaar

Werkzaamheden: F(ull-time) P(art-time) U (werkloos)

O(anders, bijv. huishouden, vrijwilligerswerk)

Beroep:

Hoogst genoten opleiding: Basisschool
 MAVO/LBO/Huishoudschool/MULO/VMBO
 MBO
 HAVO/MMS/VWO/HBS/Gymnasium), _____
 HBO/WO

Vrouwen met blaasontsteking:

Belangrijkste klachten van de vrouw:

- pijn
- verhoogde temperatuur, koorts of koude rillingen
- vaak plassen
- aandrang
- onvolledige lediging van de blaas
- bloed in urine
- verstopping (obstipatie)

Hoeveel uren of dagen heeft de vrouw al last van de klachten:----- uren/dagen

Leeftijd waarop voor het eerst blaasontsteking is opgetreden? ----- jaar/ onbekend

Seksuele activiteit in afgelopen jaar (risicofactor herhaalde blaasontsteking)

- nee
- ja, 1 partner
- ja, 2 partners
- ja, 3 of meer partners

Hormonale status van de vrouw?

- Premenopauzaal
- Postmenopauzaal (menstruatie meer dan 1 jaar geleden)

Gebruik van zelfzorgmiddelen:

- cranberry
- vitamine C (dagelijks/ alleen bij blaasontsteking)
- d-mannose
- anders, namelijk

- Diagnose huisarts:
- blaasontsteking
 - geen blaasontsteking
 - chlamydia
 - vaginale infectie
 - anders, namelijk

Antibioticumgebruik voorafgaand aan het consult? (voor behandeling of profylaxe voor blaasontsteking of voor andere indicatie)

- onbekend
- nee
- ja, namelijk

Zo ja, was het antibioticum voorgeschreven voor de huidige blaasontsteking?

- ja, voor behandeling
- ja, voor profylaxe
- nee, voor andere indicatie, namelijk

Overig antibioticumgebruik in de laatste 3 maanden?

- onbekend
- nee
- ja, namelijk (naam antibioticum en indicatie)

Is bekend welke bacterie de vorige blaasontsteking heeft veroorzaakt?

- nee
- ja, namelijk

Hoe vaak blaasontsteking in afgelopen (half)jaar?

in de laatste 12 maanden keren
 in de laatste 6 maanden keren

Analyse urine:

ochtendurine niet ochtendurine

Dipstick test: Uitgevoerd Niet uitgevoerd Niet beschikbaar

- | | | | | | | |
|----|-------------------|-----------------------------------|-------------------------------------|------------------------------------|-------------------------------------|--------------------------------------|
| a) | Nitriet: | <input type="checkbox"/> Negatief | <input type="checkbox"/> Positief + | | | |
| b) | Leucocyten (LEU): | <input type="checkbox"/> Negatief | <input type="checkbox"/> Sporen | <input type="checkbox"/> Klein (+) | <input type="checkbox"/> Matig (++) | <input type="checkbox"/> Groot (+++) |
| c) | Bloed (ERY): | <input type="checkbox"/> Negatief | <input type="checkbox"/> Sporen | <input type="checkbox"/> Klein (+) | <input type="checkbox"/> Matig (++) | <input type="checkbox"/> Groot (+++) |

Dipslide: Uitgevoerd Niet uitgevoerd Niet beschikbaar

Negatief Positief aantal CFU (colony forming units) /ml urine:

Urine sediment: Uitgevoerd Niet uitgevoerd Niet beschikbaar

Als het uitgevoerd is:

Bacteria*: 0 ± 1+ 2+ 3+ 4+

0 – Geen organismen; ± Twijfelachtig; 1+ - 1 – 10 per veld; 2+ - 10-100 per veld; 3+ - Ontelbaar, los van elkaar; 4+

- Ontelbaar, dicht op elkaar..

Urine kweek: Niet uitgevoerd Negatief Positief

Pathoog 1 (species): _____ _____ CFU/ml

Pathoog 2 (species): _____ _____ CFU/ml

Medicatie voorgeschreven voor blaasontsteking

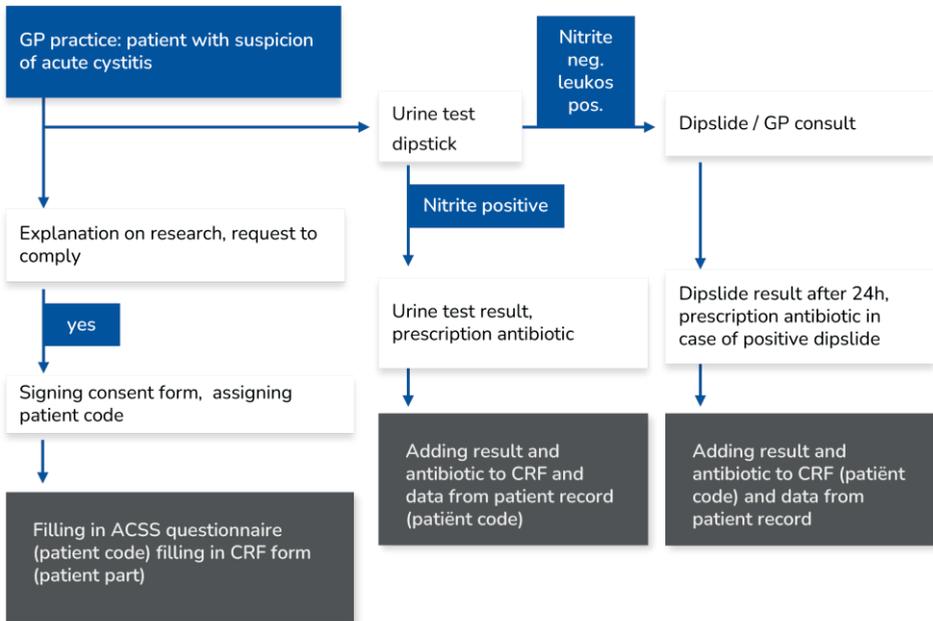
Antibioticum, namelijk _____

Andere behandeling, namelijk _____

Startdatum van de behandeling (dag/mnd/jaar): _____ / _____

Specifeer zo mogelijk
 dosering,
 aantal dagen,
 toedieningsweg

Supplement 4: Inclusion of patients with suspicion of acute cystitis in general practice



Supplement 5: Informatie voor vrouwen met vermoeden van blaasontsteking

Onderzoek van vragenlijst over blaasontsteking als vervanging voor urinetest

Veel vrouwen hebben af en toe een blaasontsteking. Meestal wordt urine bij de huisarts getest. We onderzoeken of een vragenlijst even goed werkt als een urinetest. We nodigen u uit om mee te doen aan dit onderzoek. Hartelijk dank dat u de tijd neemt om deze informatie door te nemen. Als iets niet duidelijk is, of als u meer informatie wilt hebben, kunt u dit via e-mail vragen aan de onderzoeker.

Dit onderzoek in de apotheek is een samenwerking van de Universiteit Utrecht, het LUMC (Leids Universitair Medisch Centrum) en de KNMP (organisatie van apothekers).

Waarom bent u uitgenodigd?

Vrouwen vanaf 18 jaar die met klachten van blaasontsteking bij de huisarts komen worden uitgenodigd voor dit onderzoek.

Wat is het doel van het onderzoek?

In dit onderzoek kijken we of een vragenlijst even betrouwbaar is als de urinetest. Uw ervaring en mening zijn belangrijk voor het onderzoek.

Wat verwachten we van u als u besluit mee te doen?

U wordt gebeld door de onderzoeker die u toestemming vraagt voor het raadplegen van:

- **het patiëntdossier bij uw huisarts:** u geeft toestemming om het aantal bezoeken aan de huisarts voor blaasontsteking in de afgelopen 12 maanden en gegevens over het urineonderzoek uit het dossier bij uw huisarts te halen. Ook dit wordt anoniem bewaard onder de code;
- **het medicatieoverzicht bij de apotheek:** u geeft de apotheker toestemming om aan de onderzoeker een overzicht te geven van de medicatie die u de afgelopen 3 maanden heeft gebruikt. In dit overzicht worden uw naam, adres en geboortedatum verwijderd. In plaats daarvan wordt dezelfde code gebruikt als op de vragenlijst. Zo is ook deze informatie anoniem;
- **vragenlijst:** de onderzoeker zal telefonisch met u de vragenlijst doornemen en uw antwoorden noteren. Ze kan u de vragenlijst ook mailen zodat u kunt meekijken. Het invullen van de vragenlijst kost ongeveer 5 minuten. De onderzoeker stelt u ook een aantal persoonlijke vragen. U krijgt een code van de onderzoeker voor de vragenlijst en de persoonlijke vragen, zodat uw antwoorden anoniem kunnen worden verwerkt.

Als u de vragen hebt beantwoord zal de onderzoeker u vragen of ze u na 10-14 dagen nog een keer mag bellen voor een tweede vragenformulier. We willen namelijk graag weten of uw klachten dan helemaal over zijn.

Bent u verplicht om deel te nemen

Nee, deelname aan dit onderzoek is **vrijwillig**. U mag elk moment besluiten om niet deel te nemen.

Wat gebeurt er met de resultaten van het onderzoek?

De inzichten uit het onderzoek worden gebruikt om de zorg bij blaasontsteking te verbeteren. Een samenvatting van de resultaten wordt gepubliceerd in tijdschriften.

Wat nu?

Deze informatiebrief kunt u meenemen. Als u besluit deel te nemen aan het onderzoek, wilt u dan op het formulier uw naam en telefoonnummer invullen?

U kunt het ingevulde formulier achter het formulier doen dat u invult voor de huisarts.

Onderzoeker belt u vandaag na 12.00 uur voor het invullen van de vragenlijst.

Hartelijk dank voor uw tijd en aandacht voor het doornemen van deze informatie.

Als u nog vragen heeft over het onderzoek, dan kunt u die aan onderzoeker stellen als zij u belt of via e-mail

Supplement 6: Toestemmingsformulier voor deelname ACSS-studie vrouwen met vermoeden van blaasontsteking

- Ik heb van de onderzoeker **informatie over het onderzoek naar de vragenlijst over blaasontsteking (ACSS)** gekregen. Vragen die ik had heeft de onderzoeker beantwoord. Het onderzoek is mij voldoende duidelijk.
- Ik geef toestemming voor het **anoniem verwerken van mijn antwoorden** op de vragenlijsten en op de vragen die de onderzoeker me heeft gesteld
- Ik geef toestemming aan de onderzoeker om een **geanonimiseerd medicatieoverzicht** van de laatste 3 maanden **en de uitslag van de urinetest (anoniem)** te gebruiken voor het ACSS-onderzoek
- Ik geef toestemming aan de onderzoeker om **het aantal bezoeken aan de huisarts voor blaasontsteking in de afgelopen 12 maanden uit mijn patiëntdossier** anoniem te gebruiken voor het onderzoek

Ondergetekende geeft toestemming voor deelname aan het ACSS-onderzoek:

Naam deelnemer (voorletter(s) + achternaam):

Datum:

Handtekening:

Patiëntcode:

Naam onderzoeker

Handtekening

Supplement 7: Informatie voor vrouwen zonder blaasontsteking

Onderzoek van vragenlijst over blaasontsteking als vervanging voor urinetest Veel vrouwen hebben af en toe een blaasontsteking. Meestal moet bij de huisarts urine worden ingeleverd die door de praktijkassistent wordt getest. We willen onderzoeken of de urinetest kan worden vervangen door een vragenlijst. We nodigen u uit om mee te doen aan dit onderzoek. Hartelijk dank dat u de tijd neemt om deze informatie door te nemen. Vraag het alstublieft als iets niet duidelijk is, of als u meer informatie wilt hebben. Neem de tijd om te besluiten of u mee wilt doen.

Dit onderzoek in de apotheek is een samenwerking van de Universiteit Utrecht, de KNMP en het LUMC (Leids Universitair Medisch Centrum).

Waarom bent u uitgenodigd?

Vrouwen ouder dan 18 die op dit moment geen blaasontsteking hebben en geen antibioticum gebruiken worden uitgenodigd voor dit onderzoek. Er doen 3 apotheken mee aan dit onderzoek. We hebben uw antwoorden op de vragenlijst nodig om ze te kunnen vergelijken met de antwoorden van vrouwen die blaasontsteking hebben.

Wat is het doel van het onderzoek?

Vrouwen die vaker last hebben van blaasontsteking kunnen dit meestal zelf herkennen aan hun klachten. Maar sommige klachten kunnen wijzen op een andere oorzaak. In dit onderzoek kijken we wat de betrouwbaarheid van de ACSS vragenlijst is ten opzichte van de gebruikelijke urinetest. Uw ervaring en mening zijn belangrijk voor het onderzoek.

Wat moet u doen als u besluit mee te doen?

De vragenlijst kunt u nu in de apotheek invullen. Het invullen van de vragenlijst kost ongeveer 5 minuten. U krijgt een code van de onderzoeker, zodat uw antwoorden anoniem kunnen worden verwerkt. Daarnaast heeft de onderzoeker nog een aantal aanvullende vragen voor u.

Medicatieoverzicht: u geeft de apotheker toestemming om een overzicht te maken van de medicatie die u de afgelopen 3 maanden heeft gebruikt. In dit overzicht worden uw naam, adres en geboortedatum verwijderd. In plaats daarvan wordt dezelfde code gebruikt als op de vragenlijst. Zo is ook deze informatie anoniem. De apotheker stuurt het medicatieoverzicht met code naar de onderzoeker.

Bent u verplicht om deel te nemen?

Nee, deelname aan dit onderzoek is **vrijwillig**. U mag elk moment besluiten om niet deel te nemen.

Wat gebeurt er met de resultaten van het onderzoek?

De inzichten uit het onderzoek worden gebruikt om de zorg bij blaasontsteking te verbeteren. Een samenvatting van de resultaten wordt gepubliceerd in tijdschriften.

Wat nu?

Deze informatiebrief kunt u meenemen. Als u besluit deel te nemen aan het onderzoek, wilt u dan het toestemmingsformulier invullen en tekenen?

U kunt het ingevulde en ondertekende formulier aan de onderzoeker geven.

Na het tekenen van het toestemmingsformulier krijgt u een code van de onderzoeker en kunt u de vragenlijst invullen.

Hartelijk dank voor uw tijd en aandacht voor het doornemen van deze informatie.

Als u nog vragen heeft over het onderzoek, dan kunt u die aan de onderzoeker stellen.

CHAPTER 5

General discussion

Community pharmacists are easily accessible and can provide consumers, including patients with chronic medication or potential contraindications, with appropriate counselling on the safe and effective use of nonprescription medicines, referring them to a GP as needed. Thereby, community pharmacists can improve consumers' and patients' health by counselling about minor ailments. [1-3]. They can increase patient safety because they often have access to patients' complete medication history in their pharmacy information system. They can also add nonprescription medicines to these patient records and increase GPs' awareness of nonprescription medicine usage by adding nonprescription medicines to a shared medication record, especially relevant for patients with chronic medication [4].

However, despite the potential role of the pharmacy in self-care, literature suggests room for improvement of self-care advice in pharmacy [5, 6]. Therefore, this thesis explored the current and potential future role of self-care advice in community pharmacy practice. We described facilitators and barriers to the provision of self-care advice, specifically providing insights into the opportunities for the role of community pharmacists in the treatment and prevention of recurring urinary tract infections (UTI).

Results found within this thesis

We found that Dutch community pharmacists delegate the provision of self-care advice primarily to pharmacy assistants who work under the supervision of the pharmacist (Chapter 2.1). Self-care advice in community pharmacy is based on national self-care guidelines. Within the guidelines, problem analysis is based on the WWHAM mnemonic. We found that both pharmacy assistants and community pharmacists were confident that asking out the WWHAM questions should always lead to a correct advice according to these guidelines (Chapter 2.1). In our simulated patient study (Chapter 2.2), problem analysis proved sufficient for correct advice according to the guideline on a condition-based self-care request, contrary to advice on symptom-based requests. An increasing total number of problem analysis questions was statistically significant associated with correct advice provision; additional condition-specific questions were also associated with correct advice provision (Chapter 2.2). A limited number of community pharmacists created optimal conditions

for the provision of self-care advice, such as training and assessing ready knowledge and conversation, process and analytical skills for pharmacy team members, and minimizing environmental stressors (Chapter 2.1).

Our UTI cross-sectional and longitudinal studies (Chapters 3.1 and 3.2) have shown that approximately 750.000 women (10% of all Dutch women) received antibiotic dispensings for (recurring) uncomplicated UTIs per year. Half of these women had at least one UTI recurrence over a five-year period. For diagnosis of uncomplicated UTIs, GPs rely on urinary tests (Chapter 4.1). However, we showed that diagnosis of an uncomplicated UTI might be facilitated by using the symptom-based ACSS questionnaire, on the condition that assessment of differential symptoms and specific conditions is included (Chapter 4.3).

Most women in our study recognised symptoms of a recurring UTI (Chapter 3.3). However, GP support for implementation of patient-initiated UTI treatment was limited, even with community pharmacist support (Chapter 4.1). Both GPs and community pharmacists were concerned about overuse of antibiotics by the facilitated access to UTI antibiotics (Chapter 4.1 and 4.2). Therefore, the community pharmacist's role in treating recurring UTIs should be discussed in a pharmacotherapeutic meeting with agreements on implementing and evaluating the results of pharmacists' support for patient-initiated treatment. We showed limited knowledge of women about actions to prevent recurring UTI episodes (Chapter 3.3). Therefore, information provision for women about preventive behavioural actions for recurring UTIs should be improved to decrease the number of recurring episodes.

Results of this thesis related to the COM-B model

Within this general discussion, we put the findings of the individual studies in a broader perspective, using the COM-B model [7] to understand behaviour of healthcare providers and patients in the context of self-care.

Subsequently, we provide recommendations for community pharmacists concerning self-care advice and the potential for community pharmacists' support in treating and preventing recurring UTIs.

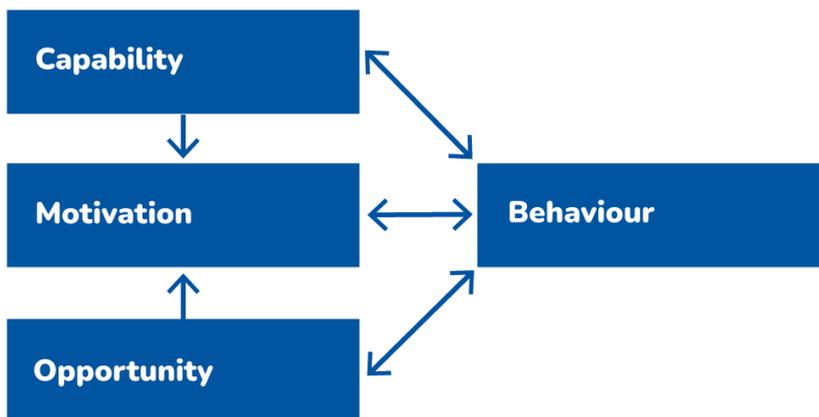
Behavioural changes in community pharmacists, including pharmacy assistants working under the supervision of the community pharmacist, and stakeholders

are required to improve self-care advice and introduce community pharmacists' support for women with recurring UTI. Nevertheless, we primarily focus on the perspective and role of the community pharmacist. The desired behaviour of the community pharmacist would be as follows:

- Community pharmacists should promote the effective and safe use of medication for condition-, product- and symptom-based self-care requests in collaboration with GPs.
- Community pharmacists should support women with recurring UTI episodes by assessing their symptoms and deciding on dispensing a UTI antibiotic, then providing information about UTI prevention in collaboration with GPs.

The COM-B model is a suitable framework to map how this desired behaviour may be achieved taking the results of the individual studies described in this thesis into account [7] (see Figure 1).

Figure 1: COM-B model, a framework for understanding behaviour



The COM-B model comprises capability, opportunity and motivation, which drive behaviour that may in turn influence these components, see Figure 1. For example, opportunity can influence motivation, as can capability, while enacting a behaviour can alter capability, motivation and opportunity.

Capability

Our study showed that reliance of community pharmacists on the WWHAM mnemonic for problem analysis (Chapter 2.1) did not lead to a correct advice in symptom-based questions (Chapter 2.2). Earlier studies have shown similar over-reliance of community pharmacists on mnemonics like WWHAM [8, 9]. When consumers present with symptom(s), pharmacy assistants first must diagnose the underlying minor ailment. Questioning on symptoms caused by ailments with overlapping symptoms should be included in problem analysis (e.g. in the case of flu-like symptoms, allergic rhinitis should be excluded) [10]. This process must occur before the self-care guideline protocol can be applied. Without diagnosing support or ready knowledge of the symptoms of minor ailments, pharmacy assistants may decide to act on the first minor ailment that comes to mind (Chapter 2.2). The alternative would be to consult the pharmacist or to refer the consumer to the GP. Notably, when consumers consult GP practices for symptoms [11], GP practice assistants use a triage tool to determine whether the GP should be consulted or whether they can refer the consumer to a pharmacy or druggist for the purchase of a nonprescription medicine [12]. Pharmacy teams require a similar minor ailment triage tool [13].

Moreover, pharmacy staff may self-assess their own behaviour with a poor to moderate level of reliability [14]. Pharmacy assistants may be inclined to skip WWHAM questions when consumers indicate by verbal or non-verbal communication that they do not need information (Chapter 2.1). Nevertheless, pharmacy assistants should ask about the person for whom the product is intended for and check whether its use is known and the dosage is correct [15]. Community pharmacists and pharmacy assistants may overestimate their ready knowledge, relying on their ability to retrieve additional information. However, when consulting a consumer at the counter, they may not search for information because it may seem unprofessional (Chapter 2.1).

Counselling follows a process of collection of relevant information, correct problem identification and adequate problem-solving and advice [16]. An accurate appraisal of answers requires ready knowledge of minor ailments, preventive behavioural actions and appropriate medicines, on which the pharmacy workforce should be trained (Chapter 2.2).

For knowledge and skills development, community pharmacists should provide regular on-the-job training and establish personal development plans for pharmacy assistants (Chapter 2.1). Moreover, pharmacy teams can discuss minor ailments and options for improvement during work meetings [17].

Furthermore, practising roleplay can improve pharmacy assistants' knowledge, conversation, process, and analysis skills [18, 19]. Roleplay can meet resistance from pharmacy assistants, most likely when they are afraid to make mistakes in front of others. Roleplay aims for participants to learn, so participants should not judge one another but provide one another with constructive feedback. Therefore, the pharmacist should lead by example and play the part of the self-care advisor first. Nevertheless, it may be preferable to have a professional leading the roleplay to minimise resistance.

Skills and knowledge can be assessed as part of an individual online training/assessment program or in simulated patient visits (Chapter 2.2) [20-23]. To learn from assessments, teams should discuss assessment results in work meetings and make arrangements to improve advising [24].

Because of a shift from reading books to consulting online publications, the guidelines, including substantiation and exercises, should be available online to provide all pharmacy assistants and community pharmacists with knowledge and background information. Moreover, changes in guideline advice should be communicated actively to community pharmacists and pharmacy assistants, and community pharmacists should discuss these changes with their teams (Chapter 2.1).

Uncomplicated UTI can be regarded as a minor ailment because in most cases a urine test suffices to diagnose an episode and many women are able to recognise symptoms of a recurring UTI episode. Nevertheless, if community pharmacists want to expand their services to self-care support for women with recurring UTIs, they should verify a recurring UTI episode as underlying cause because diagnosing based on patients' presumptions may miss potentially alarming symptoms (Chapter 4.1). Community pharmacists can use the ACSS questionnaire to verify a recurring UTI episode (Chapter 4.3) [25]. When verifying a recurring UTI episode based on the ACSS questionnaire in primary care, the community pharmacist should check whether the total typical symptoms score is 6 or higher and check scores for differential symptoms, QoL

and relevant conditions to reduce false-positive and false-negative results (Chapter 4.3). Considering pharmacy assistants' present level of self-care advice and the skills needed for assessment of the ACSS questionnaire, it seems preferable that community pharmacists verify UTI treatment requests themselves and not delegate them to pharmacy assistants (15, 16). To perform the verification check, community pharmacists may need to practice and acquire additional knowledge and skills, including clinical reasoning skills [10]. This approach will also raise GPs' trust in community pharmacists' UTI support. In the long run pharmacy technicians or designated pharmacy assistants may be trained to treat uncomplicated UTI under supervision of the pharmacist.

For prevention consultation, community pharmacists likely require a protocol and training on UTI knowledge, treatment and prevention (Chapter 4.2). Community pharmacists already may prefer to delegate a prevention consult to accredited pharmacy assistants. Counselling on UTI prevention will require clinical and pharmaceutical knowledge with training in motivational interviewing [26]. Furthermore, patient information materials should be developed with information on the risk factors for arising of acute cystitis, pharmacological and non-pharmacological treatment options and information on UTI preventive behavioural actions to support prevention counselling [27, 28].

Opportunity

Opportunity encompasses all environmental factors that may promote or hinder the desired behaviour [7]. In this thesis, we describe factors that may promote or hinder an increased role of community pharmacists in self-care advice, including UTI support. These factors are related to consumers including patients, to general practitioners, policymakers, professional bodies, healthcare insurers and pharmacy premises.

Pharmacists' support for consumers and patients

Because the population is ageing, the demand for care will increase. With a decrease in the number of practising GPs, access to GP care will become less self-evident, so consumers and patients may revert to nonprescription medicines before visiting a GP. Concurrently, polypharmacy, drug duplications and drug-drug interactions are growing concerns [29]. Although consumers may be aware of the general potential for side effects of nonprescription

medicines, they frequently lack knowledge about the interaction of nonprescription medicines with chronic medication which may lead to relevant drug-related problems, such as inappropriate self-medication, too high dosages and too long duration of use [30-33]. Community pharmacists' interventions in treating minor ailments may help decrease drug-related problems for consumers and patients, thereby decreasing overall healthcare costs [34-37].

Nevertheless, consumers and patients may not be inclined to visit the pharmacy for self-care advice because they are uncertain about the role of community pharmacists [38]. Consumers and patients are often confident about their own skills and knowledge about nonprescription medicines [11], but have less confidence in the skills and knowledge of other consumers [39]. Therefore, community pharmacists should raise awareness among consumers about self-care advice in pharmacy by providing them with appropriate, effective and safe advice to treat minor ailments and with preventive behavioural advice to prevent a return of symptoms after stopping nonprescription medicines. Apart from informing consumers in person, community pharmacists can access them via social media (e.g. in video weblogs - vlogs) and podcasts to educate them about nonprescription medicines they use (e.g. painkillers, proton pump inhibitors, acne products and morning-after pills) and (UTI) preventive behavioural actions [40]. Beyond UTI preventive behavioural actions, women's education about options such as 'wait-and-see' by using analgesics and increasing fluid intake may decrease the number of antibiotics dispensed in the pharmacy (Chapter 3.3) [41, 42].

Currently, women with recurring UTIs visit the GP practice to diagnose a UTI episode and prescribe an antibiotic (Chapters 3.3 and 4.1). In most GP practices, women must submit a urine sample before 9:00 am. They may telephone later that day for the test results and visit the pharmacy for a UTI antibiotic if the result is positive. This time-consuming procedure may suffice for some women but may be compelling for others and could lead to untimely treatment, unnecessary symptoms and work absenteeism. Moreover, women whose symptoms are not evident before 9:00 am but become bothersome later on the day have to wait until the next day for a urine test. Hence, they even may feel compelled to visit an out-of-hours clinic in the evening or during

the weekend [43], leading to increased pressure on already occupied healthcare providers.

The community pharmacist could shorten this procedure by diagnosing recurring UTIs based on the ACSS questionnaire and deciding on dispensing an antibiotic or referring the woman to the GP. If the GP and the community pharmacist agree on providing a recurring UTI antibiotic without preceding GP consultation or about the community pharmacist informing patients about UTI preventive behavioural actions, the GP should inform individual patients about this agreement.

Collaboration Community pharmacists and General practitioners

In the Netherlands, shortages of GPs are becoming apparent, especially in remote regions and in so-called deprived areas in bigger agglomerations. The growing number of GPs quitting practice by work overload exacerbates this problem [44]. In this context, community pharmacists can reduce GPs' workload by advising consumers appropriately on self-care requests [45] and by supporting women having recurring UTI.

In 2017, approximately 10% of all Dutch women [46] visited a community pharmacy at least once for a UTI antibiotic (Chapter 3.1) which shows that the number of women that call on GP practice for recurring UTI is high. However, the number of patients who consult their GP practice for recurring UTI will be even higher since not all potential UTI episodes will be confirmed by urinalysis and treated [47].

Although female patients may recognise a recurring UTI, GPs are reluctant to facilitate access to patient-initiated antibiotic treatments for the condition, even with pharmacist's support (Chapter 4.1). GPs' main concerns are losing information regarding their patients' antibiotic use, the potential to miss alarming symptoms, and the felt responsibility to diagnose and prescribe. Therefore, knowledge development of the community pharmacist, referral of patients, use of the ACSS questionnaire, electronic exchange of dispensing information and evaluation of agreements should be discussed with GPs in pharmacotherapeutic meetings (Chapter 4.1). In practice, the GP can mention patient-initiated treatments on (electronic) prescriptions, so the community pharmacist can record the agreement in the pharmacy information system and inform the GP about repeated UTI antibiotic dispensings, either directly or

through a shared dispensing record. Community pharmacists can inform women about how to prevent recurring UTI and discuss the advantages and disadvantages of self-care products such as cranberry, D-mannose and vitamin C (Chapter 4.1). Our study showed that GPs were positive about community pharmacists providing this service.

The collaboration of community pharmacists and GPs will be influenced by GPs' attitudes towards patient empowerment, work pressure and, specifically, the workload due to minor ailment consultations and existing interprofessional relationships [48]. Other causes of GP reticence may be fear of missing alarming symptoms or seeing relatively easy consultations shift to the pharmacy with only challenging and time-consuming consultations remaining. Moreover, attempts to encourage one professional group to expand or extend their practice may be perceived as a threat by other group members. To improve collaboration between GPs and community pharmacists, learning about and understanding each other's work is essential, just like the awareness of differences, the reflection on perspectives of GPs and community pharmacists, and the creation of procedures and routines clarifying tasks and responsibilities [49]. Therefore, community pharmacists should discuss perspectives of GPs and community pharmacists on self-care and recurring UTI support, make joint agreements, build confidence in GPs and facilitate the referral of consumers and patients in GP practices to the pharmacy and vice versa. Peer feedback and reflective discussions may support the community pharmacist in achieving better collaboration with GPs [49, 50]. Moreover, the alignment of guidelines on minor ailments including UTI of community pharmacists and GPs will support collaboration as well [51].

Policymakers and classification of nonprescription medicines

Reclassifying prescription medicines enlarged access to self-care medicines with nonprescription status, incentivising consumers to treat minor ailments. This reclassification was based on the patient package insert allowing consumers to safely use a nonprescription medicine for a short period. However, frequent users of nonprescription medicines, such as women, consumers older than 60 years and patients with reduced health status, prescription medicines or multi-morbidities [52], may need additional information and advice about the safe and effective use of nonprescription medicines.

Pharmacy and drugstore only (*UAD = Uitsluitend Apotheek en Drogist*) is a nonprescription medicine class. According to current law, these medicines are provided by pharmacies and drugstores, with a trained pharmacy assistant or druggist available in person for an additional explanation about medicine use. However, in recent years supermarkets started selling UAD medicines with an option for digital advice via a tablet in the supermarket given by a remote working druggist. A legal procedure started by the druggist's organisation stated that personal advice should be available to consumers. The court decided that oral or visual counselling by a remote working druggist complied with the meaning of the legislator. However, the Council of State stated that this interpretation violated the legislation's literal wordings.

The Ministry of Health could have subsequently asked the healthcare inspectorate (IGJ) to enforce healthcare law. However, the Ministry of Health did the opposite, intending to amend the law to enable UAD medication sales in supermarkets and other outlets, including petrol stations, with digital advice from a remote working druggist [53]. When such law enters into force, access to proton pump inhibitors, morning-after pills and almost all NSAIDs, including higher dosages and larger packages, without in-person advice, is facilitated. Since consumers feel confident about their skills and knowledge of nonprescription medicines [39], it is questionable whether they will ask for digital advice in a supermarket or at other points of sale. Thus, communication in pharmacy about the safe use of nonprescription medicines with patients using chronic medication and consumers with potential contraindications, becomes even more crucial.

Support from professional bodies

Professional bodies can support community pharmacists by making self-care, collaboration with GPs and pharmacy support for women with recurring UTIs an integral part of their vision for the future of community pharmacy and yearly policy plans. To support the national professional bodies in paying more interest to self-care in community pharmacy, the international pharmacists' organisation, FIP, published several reports on self-care [3, 54]. Moreover, FIP started a series of webinars in 2021 to support professional bodies with background information about self-care and a handbook for community pharmacists with information about self-care for specific minor ailments [55, 56].

Healthcare insurers and remuneration

The current system compensates community pharmacists for dispensing and care for prescription medicines. From a purely financial viewpoint, this quantity-driven system allows for the revenues of community pharmacists to increase with a higher number of prescription medicine dispensings. If informing women on preventive behavioural actions that prevent UTIs would lead to fewer antibiotic dispensings, the income of the community pharmacist would decrease, whereas the time needed to provide a prevention consultation would not be remunerated.

Similarly, community pharmacists add dispensings of self-care products to patient records and check for interactions or contraindications with chronic medication. However, these activities are currently not remunerated. Thus, preventive behavioural advice and other activities that improve the rational use of medication, including antibiotics, currently depend upon the intrinsic motivation of the community pharmacist (Chapter 2.1)[57]. Therefore, the reimbursement system should be transformed to solve these problems, for example by remunerating self-care advice or introducing population-based funding.

Pharmacy location and privacy

Co-location of a pharmacy and a GP practice (e.g. in a health centre) can facilitate clear and regular communication between the GP and the pharmacy team [58]. The layout of the pharmacy itself is crucial as well. Pharmacies increasingly have consultation rooms. Nevertheless, minor ailment consultations generally start at the pharmacy counter, while privacy at this counter is an area of concern (Chapter 2.1). Our study showed that approximately 60% of pharmacies paid sufficient attention to auditory privacy and acoustics (Chapter 2.2).

Nevertheless, consumers and patients who attach importance to what others think about them may find it challenging to enter a consultation room or receive help at a separate privacy counter (Chapter 2.1). A privacy-proof design of the counters with all counters having equal privacy by adequate distance and screens between counters would solve this problem, possibly reducing the need for a consultation room [59]. The need for an interior environment that is light, bright and airy may mislead pharmacists to place glass screens between counters, but wooden screens may be preferable

because of sound reflections. Other sound dampening options are plants, textiles and perforated panels.

Moreover, community pharmacists should discuss privacy issues with their pharmacy assistants. The pharmacy team should measure the volume of their voices or observe consultations with elderly and young patients from a seat in the waiting area. They can also provide one another with feedback to better understand consumers' and patients' privacy issues [60].

Motivation

Motivation comprise all brain processes that energise and direct behaviour, not just goals and conscious decision-making [7]. It includes habitual processes, emotional responses and analytical decisions. In this thesis, we describe the motivation of community pharmacists and pharmacy assistants.

Community pharmacists

Self-care provides community pharmacists with a unique opportunity to establish a relationship of trust with consumers even before they start using medicines. Consumers who leave the pharmacy satisfied with appropriate advice will most probably return. When asked for advice by family and friends, they may be more inclined to refer them to the community pharmacist for advice. Providing consumers with appropriate advice about safe and effective medication use may also positively impact the community pharmacists' profile as healthcare providers. For example, a community pharmacist searching for more visibility as a healthcare provider wore a short-sleeved white coat behind the counter and experienced positive reactions from patients and his pharmacy team. He noticed that patients were more patient and better listeners [61].

In our qualitative study, community pharmacists expressed the intent to support people with minor ailments, with or without providing nonprescription medicines, with preventive behavioural advice and GP referrals (Chapter 2.1). However, the focus of community pharmacists is on prescription medication, so they mostly delegate self-care advice to their pharmacy assistants while they are available for consultation in complex self-care situations (Chapter 2.1). Most community pharmacists underestimate how difficult appropriate self-care advice provision can be [62]. Studies have suggested that community pharmacists could manage most minor ailment consultations with high patient

satisfaction, yet many of them lacked the readiness to change and implement new pharmacy services [63, 64]. Several 'personality traits', relatively more common among community pharmacists, such as a lack of confidence, a fear of new responsibilities, an inability to take definitive action under 'less than textbook perfect' circumstances, a need for approval and risk-aversion, may add to this lack of readiness to implement new pharmacy services [65, 66]. In our study, only a limited number of community pharmacists created optimal conditions in the pharmacy to enable pharmacy assistants to provide appropriate self-care advice (e.g. knowledge and skills development and assessment, securing task delegation, discussing self-care advice in the pharmacy with GPs and the optimisation of logistic processes; Chapter 2.1). These community pharmacists strived for high-quality pharmaceutical care with a highly trained pharmacy team. Community pharmacists should be aware that implementing pharmacy services and creating optimal conditions for self-care advice by their pharmacy team requires both management and leadership skills [67].

Community pharmacists thought that appropriate self-care advice, with or without self-medication in the pharmacy, might prevent the development of minor ailments into chronic diseases and high costs to society (Chapter 2.1). However, they did not feel recognised in their role in the safe and effective use of self-care medication by different stakeholders. Thus, a study into the effects of self-care counselling in community pharmacy on healthcare utilisation in GP practices or qualitative studies among pharmacy visitors may increase recognition from healthcare insurers and policymakers.

A study in the UK showed that community pharmacists' decisions to provide advice on medicines newly reclassified to nonprescription status were influenced by (1) the attributes of reclassified medicines, such as benefits and risks to patients; (2) organisational and contextual factors, such as sources of information and training; (3) external factors, such as support from wider stakeholders and (4) adopter characteristics, such as community pharmacists' perceptions toward new behaviours [68]. However, in our study, most community pharmacists mentioned a lack of diagnosing skills and objections from GPs as factors against reclassifying prescription medicines to nonprescription status (Chapter 2.1). They preferred the ability to independently repeat a prescription for minor ailments that intermittently need

medication (e.g. triptans for migraine, a corticosteroid nasal spray for hay fever, hydrocortisone cream for moderate eczema and insect bites) and to monitor the effects and potential side effects of these medications with the possibility to redirect the patient to the GP if needed. Similar procedures are already in place for contraceptive pills, insulin and some other chronic medications agreed on by GPs. Thus, the option to assess a recurring UTI episode and decide on repeating a UTI antibiotic prescription for community pharmacists' support of the patient-initiated treatment of recurring UTIs may be preferable to reclassification of a UTI antibiotic or to pharmacists' prescribing authority.

Community pharmacists who have a good relationship with GPs can make agreements about reviewing a recurring UTI request using the ACSS questionnaire and repeating antibiotic prescriptions for women with recurring UTIs (Chapter 4.1). However, to maintain this good relationship, community pharmacists should discuss the results of advice (e.g. opinion of patients, prevented safety problems) in pharmacy with GPs, thereby showing their added value for prescription and self-care medicines.

In our study, community pharmacists thought they were competent to counsel women about UTI prevention and they were willing to do this (Chapter 4.2). Since the number of respondents in this study was quite low, this aspect should be investigated further before concluding.

Pharmacy assistants

Our qualitative study showed that pharmacy assistants were intrinsically motivated to help patients with minor ailments because they value providing consumers and patients with safe and effective self-care advice (Chapter 2.1). However, the priority of dispensing prescription medicines in the pharmacy leads to less attention and time for self-care advice (Chapter 2.1). If the community pharmacist wants to improve conditions for self-care advice, pharmacy assistants must be more motivated to pay attention to self-care (Chapter 2.1). Feedback from the community pharmacist, appreciation from the GP about a correct referral, and noticing that the consumer is interested in the advice in a two-way conversation add to motivation. Practising school assignments with trainees, roleplaying and taking responsibility for trainee education in the pharmacy motivate pharmacy assistants to increase their knowledge level (Chapter 2.1). Moreover, increased ready knowledge may add

to motivation by enabling pharmacy assistants to effectively provide advice within a shorter consultation time.

When pharmacy assistants function as a team, they can consult one another when encountering problems in advising a consumer, providing one another with feedback while learning from each other (Chapter 2.1). Community pharmacists can also discuss with their team when pharmacy assistants should consult them for questions about symptoms of minor ailments and complex situations [69, 70].

Conclusion

This thesis identified barriers and facilitators for community pharmacists regarding the provision of self-care advice in terms of capabilities, opportunities and motivation to achieve the desired behaviour, which led to the following practical recommendations to expand self-care advice and support for UTI patients in the pharmacy:

- The community pharmacist should strive for an optimal environment in pharmacy to improve the quality of self-care advice by arranging training and assessing knowledge and skills for themselves and their team, providing sufficient time for advice by minimising environmental stressors.
- Pharmacy assistants should know how to consult the community pharmacist in specific situations.
- Community pharmacists should improve problem analysis of symptom-based questions in pharmacy for effective self-care advice provision.
- CPs should raise public awareness among consumers and patients about how pharmacies can facilitate the safe and effective use of OTC products.
- CPs should inform consumers and patients about the background of safety related questions in the pharmacy and the reasons for recording nonprescription products in the patient file. This could improve the perception of the added value of self-care advice in the pharmacy.
- Community pharmacists should agree with GPs on content of self-care advice in pharmacy and reciprocal referral.

- To support patient-initiated treatment of recurring UTI and other minor ailments, community pharmacists should develop knowledge, skills and supporting materials, and discuss their potential role with GPs.
- Patients having symptoms of uncomplicated UTI should be informed about a wait-and-see option with ample fluid intake and painkillers to decrease the number of antibiotic dispensings.
- Community pharmacists' support for prevention of recurring UTIs can start with informing women about nonprescription preventive products (e.g. D-mannose and cranberry).

In conclusion, community pharmacists can play an important role in facilitating consumers and patients with effective self-care advice, thereby supporting them with safe and effective treatment of minor ailments, including recurring UTIs. They should raise public awareness among consumers and patients about how pharmacies can facilitate the safe and effective use of nonprescription products.

Community pharmacists also should inform patients and consumers about the background of safety related questions in the pharmacy and the reasons for recording nonprescription products in the patient file. This could improve the perception of the added value of self-care advice in the pharmacy. Nevertheless, community pharmacists should strive to create optimal conditions in pharmacy for self-care advice, such as knowledge and skills development and assessment for pharmacy assistants and community pharmacists. Community pharmacists should improve collaboration with GPs by learning about and understanding each other's work and by awareness of differences. They should reflect on the perspectives of GPs and community pharmacists on self-care and on pharmacists' support for treatment of minor ailments such as recurring UTIs and agree on procedures and routines that clarify tasks and responsibilities.

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CHAPTER 6

Summary

According to the World Health Organisation, self-care is the ability to promote health, prevent disease, maintain health and cope with illness and disability with or without the support of a healthcare provider. Promoting self-care can empower individuals, families and communities to make informed healthcare decisions, improve the efficiency of health systems and contribute to health equity.

The studies in this thesis aimed to map the current situation of self-care advice in Dutch community pharmacies. Recurring acute cystitis can be considered a minor ailment. In primary care, acute cystitis is the most common acute presentation in women. Half of the female population experiences it at least once in her lifetime. Because of the high prevalence of acute cystitis in primary care, the extensive use of antibiotics and limited attention to prevention, we focused on a potential role of the community pharmacist in treatment and prevention of recurring acute cystitis.

Current situation of self-care advice in pharmacies

In Chapter 2.1, the opinion of 13 community pharmacists' and 12 pharmacy assistants on the role of the community pharmacy in evidence-based self-care advice was studied, including barriers and facilitators for providing this advice. In total, 13 pharmacists and 12 assistants were interviewed. Pharmacists mostly delegate self-care advice provision to their assistants. Important facilitators for the provision of evidence based self-care advice were availability of guidelines, training and assessment of knowledge and skills and access to patient records. Furthermore, patient-centered communication and joint decision-making are important facilitators. Important barriers were lacking ready knowledge of minor ailments, lack of self-care collaboration between pharmacists and general practitioners, time-pressuring due to crowded waiting areas, prioritising the handling of prescribed medications above self-care advice, beliefs that WWHAM questions would always lead to correct advice and patients and consumers' trust in commercial drug information. Based on these findings, we concluded that there is room for improvement and that pharmacists by paying attention to these facilitators and barriers can strive for an optimal environment in the pharmacy for self-care advice to improve the quality of self-care advice. Pharmacists should also improve collaboration for self-care with general practitioners. Pharmacists, other healthcare providers

and government organisations should raise awareness of the importance of safe use of self-care products with consumers and patients.

The aim of the study in Chapter 2.2 was to investigate whether pharmacy assistants provide guideline-compliant advice for allergic rhinitis by studying three cases, one condition-based and two symptom-based requests. To this we used data from 673 pharmacies that participated in a pharmacy monitoring program including simulated patient visits, also known as mystery guest visits, during three years. In 2014 and 2018, problems were presented as a symptom (running nose), and the results showed that 41% and 21% of the pharmacy assistants respectively dispensed an antihistamine according to the KNMP selfcare guideline. For the condition-based problem (pet allergy) in 2016, 96% of pharmacy assistants dispensed an antihistamine according to the guideline. We studied problem analysis by calculating the number of questions asked. Both in 2014 and 2018, each additional question asked increased the chance of a correct advice. Questions asked about 'specific hay fever symptoms', 'medication', 'when symptoms occurred', and 'familiar symptoms' were most important predictors of correct advice provision. Our conclusion was that most pharmacies provided appropriate advice for a condition-based request but less than half of them provided appropriate advice for a symptom-based request. Addition of condition-specific questions to the guideline may improve the WWHAM-method.

Treatment and prevention of (recurring) acute cystitis in the Netherlands

In Chapter 3 we described two pharmacoepidemiological studies to map acute cystitis treatment in women. In Chapter 3.1 we analysed prescribing behaviour of general practitioners based on dispensings of acute cystitis antibiotics and subsequent complicated urinary tract infection by community pharmacies. To this we used dispensing data from the Dutch Foundation of Pharmaceutical Statistics for approx. 1800 community pharmacies from 2012 to 2017 at our disposal. We concluded that changes in drug preferences in the Dutch general practitioners guideline for the treatment of Urinary Tract Infection in 2013 resulted in corresponding changes in dispensed antibiotics for acute cystitis and subsequent complicated urinary tract infection with fever. However, drug choices of the antibiotics for acute cystitis differed for age categories.

Mostly, acute cystitis is a self-limiting disease that heals within a week. However, women who have had one previous acute cystitis episode are likely to experience recurring acute cystitis. The study in Chapter 3.2 aimed to investigate the yearly recurrence patterns of women aged 18 years or older returning to the pharmacy for follow-up dispensings of guideline acute cystitis antibiotics over a 5-year period. In total, more than 50% of the included women with an antibiotic dispensing in 2012 had one or more recurring antibiotic dispensings for acute cystitis in the following five years. Most of the selected women had one or more years without any acute cystitis antibiotic dispensing between the years in which they had a recurring dispensing. Approximately 2% of the selected women had one or more recurring dispensings in each year of follow up.

In Chapter 3.3 we explored self-management skills and knowledge of 719 adult women regarding behavioural actions aimed at prevention of recurring acute cystitis. Before consulting a general practice for symptoms, 32% of all women increased fluid intake and 15% of all women used analgesics and increased fluid intake. One third of all women searched the internet for information on self-management, especially women 18-51 years of age. Occasionally, 18% of all women received an antibiotic prescription for patient-initiated treatment. However, half of these prescriptions were for use if needed during vacation. Awareness of different preventive behavioural actions, such as fluid intake, complete emptying of the bladder, not postponing micturition, washing with pH-neutral soap, emptying of the bladder soon after sexual intercourse and wiping buttocks from front to back, varied between 20% and 90%. The nonprescription self-care product cranberry was used by 47% and d-mannose by 5%. Vitamin C was used by almost one third of women in spite of limited evidence for the effectiveness of vitamin C and the risk of urolithiasis.

We concluded that education of women about the use of analgesics next to increased fluid intake for selfmanagement and behavioural actions for acute cystitis prevention deserve attention.

Potential role of the community pharmacist in prevention and treatment of recurring acute cystitis

To decrease antibiotic use, on the one hand, treatment options without antibiotics should be discussed with the patient, comprising a wait-and-see policy preferably with painkillers and increased fluid intake. On the other hand, in case of recurring acute cystitis patient-initiated treatment and behavioural actions can be discussed with the patient. As GPs and practice nurses face increasing workloads, pharmacist provision of treatment for minor ailments such as recurring UTI may relieve some of the burden for GPs and their practices. Considering that community pharmacists in other countries already have a role in providing acute cystitis antibiotics to women without a preceding GP visit, we studied the possibilities for such a role in the Netherlands.

First, in Chapter 4.1 we explored general practitioners' and pharmacists' opinions regarding the desirability of patient-initiated antibiotic treatment and specifically the potential role of the community pharmacist. Patient-initiated treatment means that the patient receives a prescription from the general practitioner to use it when she experiences acute cystitis symptoms. Only one third of the general practitioners supported patient-initiated treatment and discussed this with patients. Two thirds of the pharmacists were willing to dispense an antibiotic to a patient without preceding general practitioner consultation after performing a probability check. Of the pharmacists, 70% thought that an accredited training program is necessary to gain knowledge and skills needed to assess the probability of an acute cystitis episode. Almost 50% of the general practitioners, but only 20% of the pharmacists had a preference for provision of the probability check by the pharmacist with or without pharmacy assistant' support, whereas 60% of the pharmacists preferred care provided by a pharmacy assistant with a protocol after in-service training. Both GPs and pharmacists expected a rise in antibiotic use by facilitated access without preceding GP visit. Pharmacist-facilitated access to antibiotics seems a feasible alternative only if a number of conditions are met, including discussion of general practitioner concerns, agreements with general practitioners such as feedback on dispensed antibiotics, a pharmacist acute cystitis guideline, a questionnaire for verification of symptoms and an accredited training program.

We also conducted a survey study among 78 pharmacists to study their opinion and facilitators and barriers for implementing such a counselling service (Chapter 4.2). In line with the results in Chapter 4.1, most community pharmacists were willing to counsel women about preventive actions and thought they were competent to do so. With respect to actual implementation, pharmacists foresee they will need patient information (brochure or online), a counselling protocol, and training on acute cystitis treatment and prevention as well as counselling techniques for sensitive topics.

The results in Chapter 4.1 show pharmacists prefer guidance in verifying acute cystitis. Correct diagnosis is crucial to minimise unnecessary antibiotic prescriptions since the overuse of antibiotics is recognised as the main driver of the emergence and spread of antimicrobial resistance. On the other hand, undertreatment of acute cystitis may negatively impact the quality of life and lead to a complicated urinary tract infection. The high prevalence of recurring acute cystitis in women leads to frequent general practitioner visits. Shortages of healthcare providers and diagnosing at out-of-hours primary care where antibiotics mostly are prescribed without urine test(s) urge considering more efficient ways to deal with recurring acute cystitis. An opportunity could be the use of the Acute Cystitis Symptom Score (ACSS) questionnaire which was developed to support acute cystitis diagnosis in female patients. The questionnaire assesses the severity of typical and differential symptoms, their impact on the quality of life and a number of relevant conditions in women with suspected acute cystitis to diagnose an acute cystitis episode and differentiate it from other disorders. The study in Chapter 4.3 aimed to provide insight into the congruity of acute cystitis diagnosis, measured by the ACSS questionnaire and urine test(s). In Three-quarters of patients the questionnaire result matched the urine test(s) result. This study showed that a reduction in false-positive and false-negative results of the questionnaire can be achieved by including scores for differential symptoms, quality of life scores, relevant conditions and moderate or severe scores for blood in the urine in the evaluation of the questionnaire. Moreover, a reduction in false-negative results of urine test(s) is possible by including the total typical symptoms score and quality of life scores from the questionnaire in diagnosing. The added value of the ACSS questionnaire in Dutch clinical practice is that the ACSS questionnaire can be filled in easily and fast by most women and can save

contact time in primary care. The questionnaire provides information on seriousness of symptoms, on differential symptoms irrespective of the time of day women visit the practice for symptoms of acute cystitis. Thus, it may not only improve acute cystitis diagnosis in general practice but also in out-of-hours primary care and verification by trained community pharmacists.

Conclusion and recommendations

Community pharmacists can play an important role in self-care by facilitating consumers and patients with effective advice, thereby supporting them with safe and effective treatment of minor ailments, including recurring acute cystitis. Because of that they can decrease general practice workload. Healthcare providers, healthcare organisations and government organisations should raise awareness among consumers and patients about safe and effective use of nonprescription medicines. Community pharmacists should also raise public awareness about their potential in providing patients with self-care advice including preventive actions. They should inform patients and consumers about the background of safety related questions in the pharmacy and the reasons for recording nonprescription medicines in the patients file. This could improve the perception of the added value of self-care advice in pharmacy. To be able to do this, community pharmacists should strive for optimal conditions in pharmacy for self-care advice, such as knowledge and skills development and assessment of self-care advice for themselves and their team. Community pharmacists could improve collaboration with general practitioners in self-care by learning about and understanding each other's work and by awareness of differences. General practitioners and community pharmacists could reflect on their perspectives on self-care. They could also discuss pharmacists' support for treatment of minor ailments such as recurring acute cystitis and agree on procedures and routines that clarify tasks and responsibilities.

Nederlandstalige Samenvatting

Volgens de Wereldgezondheidsorganisatie (WHO) is zelfzorg is het vermogen om gezondheid te bevorderen, ziekte te voorkomen, gezond te blijven en om te gaan met ziekte en handicaps met of zonder de ondersteuning van een zorgverlener. Het bevorderen van zelfzorg kan personen, families en gemeenschappen in staat stellen om goed geïnformeerd beslissingen te nemen over (zelf)zorg, het kan de doelmatigheid van de gezondheidszorg verbeteren en bijdragen aan gelijkheid in de gezondheidszorg.

Het doel van de studies in dit proefschrift was om de stand van zaken van zelfzorgadvisering in Nederlandse openbaar apotheken te in kaart te brengen. Herhaalde blaasontsteking bij vrouwen kan beschouwd worden als een kleine kwaal. Blaasontsteking is de meest voorkomende acute aandoening in de eerstelijnszorg. De helft van de vrouwen krijgt het ten minste een keer in hun leven. Gezien de hoge prevalentie van blaasontsteking bij vrouwen in de eerstelijnszorg, het omvangrijke gebruik van antibiotica en beperkte aandacht voor preventie hebben we ons met name gericht op een potentiële rol van de openbaar apotheker bij de behandeling en preventie van herhaalde blaasontsteking bij vrouwen.

De huidige stand van zaken van zelfzorgadvisering in de apotheek

In Hoofdstuk 2.1 is de mening van 13 apothekers en 12 apothekersassistenten over de rol van de openbaar apotheek bij evidence-based³ zelfzorgadvisering onderzocht, inclusief de factoren die het geven van dit advies makkelijker maken of juist belemmeren. Apothekers delegeren het geven van zelfzorgadviezen veelal aan hun assistenten. Belangrijke factoren die het geven van evidence-based¹ zelfzorgadvies bevorderen waren beschikbaarheid van zelfzorgstandaarden, training en toetsing van kennis en vaardigheden in de praktijk en toegang tot het patiëntendossier. Verder is patiëntgerichte communicatie en gezamenlijke besluitvorming belangrijk.

Belangrijke belemmeringen waren het ontbreken van parate kennis over kleine kwalen, gebrek aan samenwerking tussen apotheker en huisarts op het gebied van zelfzorg, tijdsdruk door drukte in de wachtruimte, het geven van voorrang

³ Evidence-based = op bewijs gebaseerd

aan receptmedicatie, het geloof dat het stellen van de WHAM-vragen⁴ en vragen naar de klachten altijd zou leiden tot een correct advies en het vertrouwen van consumenten in commerciële medicijninformatie. Op basis van deze bevindingen concludeerden we dat er ruimte is voor verbetering en apothekers door aandacht te hebben voor deze bevorderende en belemmerende factoren kunnen streven naar een optimaal klimaat voor zelfzorgadvies in de apotheek om de kwaliteit van het zelfzorgadvies te verbeteren. Apothekers zouden de samenwerking met huisartsen moeten verbeteren. Ook zouden apothekers en andere zorgverleners en overheidsorganisaties consumenten bewust moeten maken van het belang van veilig gebruik van zelfzorgmiddelen.

De studie in Hoofdstuk 2.2 had als doel om te onderzoeken of apothekersassistenten adviseren volgens de zelfzorgstandaard bij drie casussen van allergische rinitis: een casus gebaseerd op een vraag over de aandoening allergie en twee vragen gebaseerd op symptomen van allergie. Hiervoor maakten we gebruik van gegevens van 673 openbaar apotheken die gedurende drie jaren deelnamen aan een apotheek monitoring programma met mystery guest-onderzoeken. In 2014 en 2018, werd het probleem gepresenteerd als een symptoom (loopneus) en de resultaten lieten zien dat respectievelijk 41% en 21% van de apothekersassistenten een antihistaminicum verstreekte in overeenstemming met de zelfzorgstandaard Allergische rinitis. Voor de vraag over de aandoening in 2016 (huisdierallergie), verstreekte 96% van de apothekersassistenten een antihistaminicum volgens de standaard. Om de probleemanalyse te bestuderen hebben we het aantal gestelde vragen berekend. Naarmate het aantal gestelde vragen toenam, steeg zowel in 2014 als in 2018 de kans op een advies volgens de zelfzorgstandaard. De belangrijkste voorspellers van een correct advies waren vragen over 'specifieke hooikoorts symptomen', 'gebruik van andere medicatie', 'wanneer de symptomen optraden' en 'bekendheid met de symptomen'. Onze conclusie was dat bijna alle apotheken een passend advies gaven voor een vraag naar iets voor een kwaal maar dat minder dan de helft van de apotheken een passend advies gaf voor een vraag over een symptoom. Het toevoegen

⁴ WHAM-vragen zijn: voor Wie is het advies/het zelfzorgmiddel bedoeld, Hoe lang heeft de klant al last van de klachten, welke Actie heeft de klant zelf al ondernomen en andere Medicatie die gebruikt wordt

aan de zelfzorgstandaard van vragen die specifiek zijn voor een kleine kwaal zou de WHAM-methode kunnen verbeteren.

Behandeling en preventie van (herhaalde) blaasontsteking bij vrouwen

In Hoofdstuk 3 beschreven we twee farmacoepidemiologische studies⁵ om de behandeling van blaasontsteking bij vrouwen nader in kaart te brengen. In Hoofdstuk 3.1 analyseerden we het voorschrijfgedrag van huisartsen op basis van verstrekkingen in de openbaar apotheek van antibiotica voor blaasontsteking⁶ en voor verstrekking van antibiotica voor een gecompliceerde hogere urineweginfectie⁷ binnen 14 dagen hierna (als het antibioticum voor blaasontsteking onvoldoende of niet gewerkt zou hebben). Voor dit onderzoek maakten we gebruik van de gegevens van de Stichting Farmaceutische Kengetallen (SFK) met aflevergegevens van ong. 1800 openbaar apotheken van 2012 tot en met 2017. Onze conclusie was dat veranderingen van de voorkeursantibiotica in de NHG standaard Urineweginfecties resulteerden in vergelijkbare veranderingen in de afgeleverde antibiotica voor blaasontsteking en gecompliceerde urineweginfectie in Nederlandse apotheken. Welke antibiotica voor blaasontsteking werden voorgeschreven bleek echter ook afhankelijk van de leeftijd van de vrouw.

Blaasontsteking geneest meestal spontaan binnen een week. Maar vrouwen die eerder blaasontsteking hebben gehad, hebben kans op herhaling van blaasontsteking. In de studie van Hoofdstuk 3.2 wilden we het jaarlijks herhalingspatroon van de verstrekking van antibiotica voor blaasontsteking over een periode van 5 jaar onderzoeken bij vrouwen van 18 jaar en ouder die na een eerste verstrekking⁸ terugkwamen in de apotheek voor een antibioticum voor blaasontsteking⁴. In totaal had meer dan de helft van de vrouwen met een eerste verstrekking van een antibioticum voor blaasontsteking in 2012 een of meer herhaalde verstrekkingen voor een antibioticum voor blaasontsteking in de daarop volgende vijf jaren. De meeste vrouwen hadden een of meer jaren

⁵ Farmaco-epidemiologie bestudeert de rol van geneesmiddelen in relatie tot ziekten.

⁶ Antibiotica voor blaasontsteking: nitrofurantoïne, fosfomycine, trimethoprim

⁷ Antibiotica voor een gecompliceerde hogere urineweginfectie: ciprofloxacin, amoxicilline/clavulaanzuur, co-trimoxazol

⁸ Eerste verstrekking = geen antibioticum in de 12 maanden daarvoor

zonder antibioticum tussen de jaren waarin ze opnieuw voor een antibioticum voor blaasontsteking in de apotheek kwamen. Ongeveer 2% van de vrouwen kwam elk jaar in de apotheek voor een of meer verstrekkingen van een antibioticum voor blaasontsteking.

De studie beschreven in Hoofdstuk 3.3 gaat in op het zelfmanagement van blaasontsteking en de kennis van 719 vrouwen over preventieve maatregelen om blaasontsteking te voorkomen. Voordat vrouwen de huisarts raadpleegden vanwege symptomen van blaasontsteking ging 32% van hen meer drinken en 15% gebruikte pijnstillers in combinatie met meer drinken. Een derde van alle vrouwen zocht op internet naar informatie over wat ze zelf konden doen bij blaasontsteking, met name vrouwen tussen 18 en 51 jaar. Van alle vrouwen kreeg 18% wel eens een extra recept voor een antibioticum om te gebruiken als ze symptomen van blaasontsteking hadden. Bij de helft van deze vrouwen was het recept voor zo nodig gebruik tijdens vakantie. Bekendheid van vrouwen met de verschillende maatregelen om blaasontsteking te voorkomen, zoals meer drinken, de blaas helemaal leegmaken, plassen niet uitstellen, het leegmaken van de blaas na seks en de billen afvegen van voor naar achter, varieerde van 20 tot 90%. Vrij verkrijgbare cranberryproducten werden gebruikt door 47% en d-mannose door 5% van de vrouwen. Bijna een derde van de vrouwen gebruikte vitamine C ondanks beperkt bewijs dat het werkt en de kans op het ontstaan van nierstenen. Onze conclusie was dat voorlichting van vrouwen over het gebruik van vrij verkrijgbare pijnstillers, meer drinken als zelfbehandeling en over preventieve maatregelen aandacht verdienen.

Mogelijke rol van de openbaar apotheker bij voorkomen en behandeling van herhaalde blaasontsteking

Om het gebruik van antibiotica te verminderen, zouden behandelopties zonder antibiotica, zoals een afwachtend beleid, bij voorkeur met pijnstillers en meer drinken, met de patiënt besproken moeten worden. Bij herhaalde blaasontsteking kunnen ook preventieve maatregelen en het door de patiënt zelf starten van antibioticumgebruik worden besproken. Aangezien de werkdruk voor huisartsen en praktijkassistenten toeneemt, zou de behandeling van kleine kwalen zoals herhaalde blaasontsteking de werkdruk van huisartsenpraktijken enigszins kunnen verlichten. In andere landen hebben openbaar apothekers al een rol bij de behandeling van blaasontsteking door

verstrekking van antibiotica zonder voorafgaand bezoek aan de huisarts. Derhalve hebben wij de mogelijkheden voor een dergelijke rol van de openbaar apotheker in Nederland bestudeerd.

In Hoofdstuk 4.1 onderzochten we de mening van huisartsen en apothekers over het eventueel door de patiënt zelf starten van de behandeling met antibiotica (= patient-initiated treatment) en daarbij in het bijzonder de rol die de openbaar apotheker kan spelen hierin. Dit betekent dat de patiënt een recept van de huisarts krijgt om te gebruiken wanneer deze op basis van de symptomen last denkt te hebben van blaasontsteking. Slechts een derde van de huisartsen was voorstander van door de patiënt zelf gestart gebruik van antibiotica en gaf ook aan dit met de patiënt te bespreken. Twee derde van de apothekers was bereid om na het uitvoeren van een check of er inderdaad sprake is van blaasontsteking, een antibioticum te verstrekken zonder voorafgaand bezoek aan de huisarts. Van de apothekers dacht 70% dat een geaccrediteerde training nodig is om kennis en vaardigheden aan te leren die nodig zijn om blaasontsteking vast te kunnen stellen. Voor het uitvoeren van de check op blaasontsteking had bijna 50% van de huisartsen de voorkeur voor uitvoering door de apotheker met of zonder ondersteuning van een assistent terwijl slechts 20% van de apothekers hier de voorkeur aan gaf. De voorkeur van 60% van de apothekers was voor uitvoering van de check door een apothekersassistent met een protocol na het volgen van een training. Zowel huisartsen als apothekers verwachtten een stijging van antibioticumgebruik bij laagdrempeliger toegang tot antibiotica, dus zonder voorafgaand bezoek aan de huisarts. Door de apotheker ondersteunde laagdrempeliger toegang tot antibiotica lijkt alleen haalbaar als aan een aantal voorwaarden wordt voldaan, waaronder bespreking van de bedenkingen van de huisarts, afspraken met huisartsen bijvoorbeeld over terugkoppeling van verstrekte antibiotica, een richtlijn over blaasontsteking voor de apotheker, een vragenformulier voor verificatie van de symptomen en een geaccrediteerde training.

We hebben ook een vragenlijstonderzoek uitgevoerd onder 78 apothekers om de bereidheid en de bekwaamheid van apothekers om vrouwen te adviseren over preventie van blaasontsteking te bestuderen (Hoofdstuk 4.2). In lijn met de resultaten van Hoofdstuk 4.1 waren de meeste apothekers bereid om vrouwen te adviseren over preventieve maatregelen en dachten ze dat ze de

voldoende vaardigheden hadden om dat te doen. Voor implementatie denken apothekers patiëntinformatie (folder of online), een gespreksprotocol, een training over behandeling, preventie van blaasontsteking en adviesvaardigheden voor gevoelige onderwerpen nodig te hebben.

De resultaten van Hoofdstuk 4.1 laten zien dat apothekers de voorkeur geven aan ondersteuning voor het verifiëren van blaasontsteking. Een correcte diagnose is belangrijk om onnodige antibioticum recepten te minimaliseren aangezien overmatig gebruik van antibiotica wordt gezien als de belangrijkste factor voor het ontstaan en de verspreiding van antibioticaresistentie. Aan de andere kant kan onderbehandeling van blaasontsteking negatieve gevolgen hebben op de kwaliteit van leven en leiden tot een gecompliceerde hogere luchtweginfectie. Doordat herhaalde blaasontsteking vaak voorkomt, leidt dit tot veelvuldig bezoek aan de huisartspraktijk. Tekorten aan zorgverleners en diagnostisering bij avond- en weekenddiensten waar antibiotica meestal worden voorgeschreven zonder urinetest(s) zijn aanleiding voor het zoeken naar efficiëntere manieren om met blaasontsteking om te gaan. Een mogelijkheid zou het gebruik van de Acute Cystitis Symptom Score (ACSS) vragenlijst kunnen zijn die is ontwikkeld om diagnostiek van blaasontsteking bij vrouwen te ondersteunen. In de vragenlijst worden de ernst van de gebruikelijke en andere differentiële klachten vastgelegd, hun invloed op de kwaliteit van leven en een aantal relevante aandoeningen om blaasontsteking te kunnen verifiëren en het te onderscheiden van andere aandoeningen. De studie in Hoofdstuk 4.3 is uitgevoerd om de overeenstemming van de diagnose van blaasontsteking tussen twee methoden te bestuderen, namelijk de ACSS vragenlijst en de urinetest(s) bij de huisarts. Bij driekwart van de patiënten kwam het resultaat van de vragenlijst overeen met de urinetest(s). Deze studie liet zien dat het aantal vals positieve en vals negatieve resultaten van de ACSS vragenlijst kan worden verminderd door in de beoordeling de scores voor andere klachten, kwaliteit van leven, relevante aandoeningen en tamelijk ernstige of ernstige scores voor bloed in de urine mee te nemen. Maar ook vals negatieve resultaten van de urinetest(s) kunnen met de vragenlijst worden verminderd door bij de evaluatie de totaalscore van gebruikelijke klachten en de score van kwaliteit van leven uit de vragenlijst mee te nemen in de diagnose. De toegevoegde waarde van de ACSS vragenlijst in de Nederlandse situatie is dat de meeste vrouwen de vragenlijst gemakkelijk en snel kunnen

invullen en dat het contacttijd kan besparen in de eerstelijns. De vragenlijst verschaft informatie over de ernst van gebruikelijke en differentiële symptomen onafhankelijk van het tijdstip op waarop de vrouw met verdenking van blaasontsteking in de praktijk komt. Derhalve kan het niet alleen de diagnostiek van blaasontsteking in de huisartspraktijk verbeteren maar ook in de avond- en weekenddienst en de verificatie door daarvoor opgeleide openbaar apothekers.

Conclusie en aanbevelingen

Openbaar apothekers kunnen een belangrijke rol spelen bij zelfzorg door het ondersteunen van patiënten en consumenten met doeltreffende adviezen, en hen daardoor ondersteunen bij een veilige en effectieve behandeling van kleine kwalen, inclusief herhaalde blaasontsteking. Apothekers kunnen zodoende de werkdruk van de huisarts verminderen. Zorgverleners, organisaties in de gezondheidszorg en overheidsorganisaties zouden consumenten bewust moeten maken van het belang van veilig gebruik van zelfzorgmiddelen. Openbaar apothekers zouden ook meer bekendheid moeten geven aan hun mogelijkheden om patiënten te adviseren over zelfzorg voor kleine kwalen inclusief preventieve maatregelen. Ze zouden patiënten en consumenten moeten informeren over de reden waarom ze vragen stellen voordat ze een advies kunnen geven en over de reden waarom ze zelfzorgmiddelen vastleggen in het patiëntdossier. Dit zou het beeld over de toegevoegde waarde van zelfzorgadvies in de apotheek kunnen verbeteren. Om dit te kunnen doen moeten openbaar apothekers streven naar een optimaal klimaat in de apotheek voor het verlenen van zelfzorgadvies zoals ontwikkeling van kennis en vaardigheden en toetsing van advisering voor henzelf en hun team. Openbaar apothekers zouden de samenwerking met huisartsen op het gebied van zelfzorg kunnen verbeteren door het leren over en begrijpen van elkaars werk en door zich bewust te zijn van de verschillen. Apothekers en huisartsen zouden kunnen reflecteren op hun kijk op zelfzorg. Daarnaast zouden ze ondersteuning door de apotheker voor de behandeling van kleine kwalen zoals herhaalde blaasontsteking kunnen bespreken en afspraken maken over werkwijze en procedures die taken en verantwoordelijkheden verduidelijken.

CHAPTER 7

Appendices

Dankwoord

In 2016 kreeg ik het aanbod om als afsluiting van mijn carrière promotieonderzoek te gaan doen. Kees de Blaey had me vroeger weleens gevraagd of ik onderzoek wilde gaan doen maar met het in deeltijd managen van het GIC en de thuissituatie zag ik daar destijds geen mogelijkheden voor. Nu echter zag ik promoveren als een uitdaging, iets wat ik nog niet eerder had gedaan. Het moest wel onderzoek zijn dat zou kunnen leiden tot verbetering van zorg voor patienten. Dat is namelijk altijd mijn intrinsieke motivatie geweest en ik weet hoe belangrijk het is om dingen te doen waar je energie van krijgt. En dat was niet moeilijk want het eerste onderwerp dat in me opkwam was zelfzorg. Na het ontwikkelen van de zelfzorgstandaarden en het implementeren daarvan had ik nu de kans om te onderzoeken hoe de stand van zaken van zelfzorgadvisering in de praktijk was. Als snel had ik vier onderwerpen om te onderzoeken op het gebied van zelfzorg, waar blaasontsteking er een van was. Ik had gezien dat apothekers in het buitenland een rol kregen bij de behandeling van vrouwen met blaasontsteking. En toen ik bij een KNMP-jubileum van Douwe Breimer het advies kreeg om te focussen, was de keuze voor blaasontsteking als focusonderwerp de meest logische.

Het was een intensief traject dat ik alleen met steun van heel veel mensen in mijn omgeving en netwerk heb kunnen uitvoeren. Daarvoor wil ik hen hartelijk bedanken.

Als eerste mijn promotieteam, bestaande uit Marcel Bouvy, Martina Teichert en Ellen Koster, voor hun begeleiding en onze maandelijkse overleggen.

Beste Marcel, toen ik je vertelde over mijn voornemen om promotieonderzoek naar zelfzorg te gaan doen reageerde je meteen enthousiast en was ook bereid om mijn promotor te worden. Je hebt een brede belangstelling, kennis en ervaring maar hebt de neiging je bordje (over)vol te laden. Daar had ik soms best wel moeite mee. Maar hoewel ik er vaak lang op moest wachten en er de nodige herinneringsmails aan voorafgingen, kwam er altijd uniek en opbouwend commentaar als jij als laatste naar een manuscript keek. Je keek er net even anders naar en tilde de kwaliteit van het manuscript nog een treetje hoger. In de eerste jaren vergaderden we in Leiden en na afloop hadden we vaak gesprekken over de farmaceutische zorg in het algemeen. COVID-19 verhinderde continuering daarvan uiteraard maar over prangende kwesties hebben we daarna via e-mail gecommuniceerd. Ik heb dat zeer gewaardeerd. En bij de etentjes bij Ellen heb ik gemerkt dat je echt een apotheker bent: je kunt heel lekkere en originele desserts maken. Onlangs ben je begonnen als

hoofd van het departement Farmaceutische Wetenschappen. Ik wens je veel succes in deze nieuwe functie.

Beste Martina, we waren collega's bij de KNMP toen ik je vroeg of je co-promotor wilde worden. Je vond dat een eer en ik hoop dat dat ook bewaarheid is geworden. Ik vond het heel fijn dat je me in het begin van mijn promotietraject intensief hebt geholpen met de opzet en searches voor de epidemiologische onderzoeken. Je hebt me geleerd dat ik voor een publicatie keuzes moet maken in de resultaten die ik, zeker bij de eerste onderzoeken, in de analysefase had verzameld. Bedankt voor je grondige commentaren op alle manuscripten. Aan je stijl van commentaar geven moest ik in het begin erg wennen maar ik merkte de afgelopen jaren dat je mails met commentaar in positieve zin zijn veranderd. Bedankt ook voor de gezellige etentjes waarin we van alles en nog wat konden bespreken, van voorstellingen tot recepten. Het auberginerecept heb ik een aantal malen gemaakt en was een groot succes.

Beste Ellen, vanaf het APIOS-project ben jij als co-promotor aangeschoven. De manuscripten gingen vanaf die tijd als eerste naar jou en het commentaar kwam meestal snel retour. Als het niet op korte termijn lukte liet je me weten wanneer ik het wel kon verwachten. Dat heb ik zeer gewaardeerd. Dank ook voor de gezellige etentjes met fantastisch lekker eten waar ik (als buitenpromovendus) mijn medepromovendi kon ontmoeten. Binnenkort begin je met een nieuwe uitdaging als senior beleidsadviseur bij de internistenvereniging. Met jouw capaciteiten twijfel ik er niet aan dat ook dat een succes wordt.

Beste Bill, toen ik begon aan mijn onderzoek veranderde je rol van gewaardeerde collega in aanspreekpunt voor mij binnen de KNMP. Bedankt voor het mogen volgen van trainingen en het inzetten van stagiaires op mijn onderzoeken. Na je vertrek bij de KNMP merkte ik hoezeer ik onze bijpraatsessies miste. Ik wens je veel succes in je verdere carrièrestappen.

Beste Maayke en Mieke, in jullie KNMP-bestuursjaren werkten we al samen aan zelfzorg. Dat hebben we de afgelopen jaren kunnen continueren. Bedankt daarvoor.

Maayke, de afgelopen jaren hebben we regelmatig bijgepraat over zelfzorg en ik bewonder je mateloos enthousiasme en uithoudingsvermogen om dit onderwerp bij verschillende stakeholders telkens weer een stapje verder te brengen. Een opmerking van jou tijdens een van onze gesprekken heeft me

gemotiveerd om te kijken naar het onderwerp blaasontsteking. Bedankt hiervoor. Ik verheug me op de webcast.

Mieke, je was altijd bereid om tijd vrij te maken als ik je vroeg om mee te werken aan een onderzoek. Ik heb veel van je geleerd, bedankt daarvoor.

Beste Monique, samenwerken met jou was altijd een feestje met als sluitstuk de LESA chronische medicatie. Bedankt voor alle informatie over het voorschrijfsysteem van de huisartsen en dat je Amanda hebt vrijgemaakt voor de commentaarrronde zodat ik het APIOS-onderzoek kon voorbereiden. Beste Amanda, bedankt voor je toewijding en energie in de laatste fase van de LESA, ik heb het zeer gewaardeerd.

Beste Fabienne en adviesraad van SFK, dank voor de toestemming voor het gebruik van SFK-data. Beste Manon en Petra, bedankt voor het uitzoeken van aanvullende data die ik nodig had voor de referentencommentaren.

Beste Karen, toen ik manager van het GIC was vond ik de gesprekken met jou over de apotheekpraktijk altijd heel motiverend en inspirerend. We hebben in die tijd de KennisTest ontwikkeld en de LESA's waar je je ervaring en kennis uit de praktijk inbracht. Toen ik inbreng uit de praktijk nodig had voor voorbereiding en testen van vragenlijsten bij mijn onderzoeken was jij dan ook een logische keuze. Bedankt voor je medewerking.

Beste Annemieke, bedankt voor je medewerking aan mijn onderzoek en met name voor alle artikelen die je voor me hebt gevonden in de eerste jaren toen ik nog geen toegang had tot de UU bibliotheek.

Beste Bart, bedankt voor het delen van je ervaringen in de apotheek en je feedback voor mijn onderzoeken.

Beste Caroline, in mijn eerste onderzoeksjaar vroeg je me om een onderzoek voor APIOSsen te ontwerpen. Ik weet dat dit onderzoek je veel tijd heeft gekost, mede omdat alle feedback naar de APIOSsen via jou verliep. Bedankt voor al je inspanningen, het heeft mooie publicaties opgeleverd.

Dank ook aan de patienten, apothekers en huisartsen die met mij hun ervaring met de behandeling en preventie van blaasontsteking wilden delen. En natuurlijk ook alle APIOSsen, apotheker opleiders en huisartsen die aan dit onderzoek hebben meegewerkt, bedankt daarvoor.

Beste Hetty en Kees, bedankt voor jullie enthousiasme voor mijn onderzoek en dat ik data uit jullie bestand mocht gebruiken. Het leverde mooie resultaten en dito publicatie op.

Beste Daphne, bedankt voor je ondersteuning bij het opzetten van de online preventievragenlijst en het aanleveren van de data. Ook dank aan de apothekers die deze vragenlijst hebben getest.

Bij een aantal onderzoeken heb ik ondersteuning gekregen van de masterstudenten Danielle, Valerie en Devika. Bedankt voor jullie inzet en toewijding tijdens jullie onderzoeksstage. Valerie en Devika, jullie hebben de nodige problemen ondervonden door COVID-19. Valerie, jij moest na een korte periode het onderzoek in de praktijk staken en hebt toen een ander onderzoek opgepakt. Devika, jij hebt het onderzoek waar Valerie mee gestart was weer opgepakt op een andere locatie maar met de nodige aanpassingen die het includeren van patiënten bemoeilijkte. Bedankt voor jullie flexibiliteit. Ik vond het een plezier om jullie te begeleiden en met jullie samen te werken.

Dear Kurt and Jakhongir, many thanks for allowing me to translate the ACSS questionnaire and study it in primary care. I appreciated cooperating with you and I am much obliged to you for promptly answering my questions and your contribution to the manuscript, specially the figures in R from Jakhongir.

Beste Rob, een native speaker in Engels en Nederlands. Een betere vertaler kon ik me niet wensen, bedankt.

Beste Fleur, Marieke, Elze en Henk-Frans, bedankt voor jullie bereidheid om vanuit de huisarts- en apotheekpraktijk mee te werken aan het ACSS vragenlijstonderzoek.

Beste Marion, we hebben samengewerkt aan de eerste en laatste LESA. Ik heb je mogen interviewen voor het APIOS onderzoek en voor het ACSS-onderzoek hebben we meermalen overlegd over de mogelijke oorzaken van afwijkende resultaten van urinetest en vragenlijst. Ik heb hier heel veel van geleerd en heb weer eens gezien hoe belangrijk het is om niet alleen naar een testuitslag of de totaalscore van de gebruikelijke symptomen te kijken maar ook naar mogelijke symptomen van andere klachten. Ook heb ik meer inzicht gekregen in de overbelasting van huisartsen. Volgens mij hebben patiënten in jou een heel goede huisarts en ik hoop voor hen dat je die zorg nog lang kunt bieden.

Beste Bart, in de startfase van het project heb je het formulier met patiëntdata en de vragenlijst becommentarieerd. Ook heb je me inzicht gegeven in welke huisartsdata zinvol waren om uit te vragen. Bedankt daarvoor.

Verder wil ik alle vrouwen, met en zonder ervaring met blaasontsteking, bedanken die een bijdrage hebben geleverd aan de vertaling en de cognitieve validatie van de ACSS vragenlijst.

Dank ook aan alle apothekers en apothekersassistenten die ik heb mogen interviewen voor het kwalitatief onderzoek en hun bereidheid om niet alleen hun goede maar ook minder goede ervaringen met zelfzorg in de praktijk te delen.

Beste Jeroen en Marle, tijdens mijn PhD traject heb ik met jullie het meeste contact gehad. Bedankt voor jullie steun en betrokkenheid. Verder wil ik Josephine, Tristan, Lisa, Laura, Jacqueline en Ruby bedanken voor de leuke gesprekken tijdens incidentele contacten en hun veel succes wensen bij hun verdere onderzoek. Beste Marnix, we hebben de nodige mails uitgewisseld over onze voortgang en ik hoop dat ook jij je promotieonderzoek binnenkort kunt afronden.

Beste Remco en Aldo, bedankt voor de ICT-ondersteuning die ik vooral in de beginperiode nodig had voor gebruik van KNMP Parallels.

Beste Reinier, dank voor je ondersteuning bij de APIOS-vragenlijsten.

Beste Ton, bedankt voor de bestanden voor de epidemiologische studies en je hulp bij het zoeken naar de oorzaak als een uitdraai anders uitpakte dan we verwacht hadden.

Paulien en Wilma, tijdens FIP in Buenos Aires vertelde ik jullie over mijn plan om promotieonderzoek te gaan doen. Jullie vonden dat een uitstekend plan en Wilma heeft me duidelijk gemaakt hoe leuk het is om onderzoek te doen. Dank daarvoor, het was inderdaad leuk en ik heb heel veel bijgeleerd. Paulien, bedankt ook voor de gezellig bijpraat tijdens etentjes en lunches. Ik vond het heel gezellig. Wilma, jou wens ik veel succes met de afronding van je promotieonderzoek.

Beste Annette en Fokko, niet alleen tijdens mijn werk als manager maar ook tijdens dit onderzoekstraject heb ik heel veel gehad aan jullie trainingen. Ik geniet nog wekelijks van de zondagse bespiegelingen van Fokko op LinkedIn. Bedankt voor jullie steun.

Beste Gabi, volgens mij tennissen we al zo'n 20 jaar samen en in die tijd heb je mijn wel en wee meegemaakt. Bedankt voor je steun en luisterend oor. Ik hoop dat we nog lang samen kunnen spelen.

Verder wil ik Jeanne, Monique, Marjolein, Marjolein, Trudi, Jet, Janneke, Geisa en Li Lian bedanken voor de sportieve, ontspannen en gezellige tenniswoensdagochtenden.

Verder wil ik alle verdere vrienden en bekenden bedanken voor hun belangstelling voor mijn onderzoek. Iedereen kende wel iemand die last had van blaasontsteking en het bevestigde voor mij het belang van mijn onderzoek.

Lieve Betty, je bent een zus uit duizenden. Bedankt voor je luisterend oor, voor de gezellige uitstapjes en de lunches en etentjes. Volgend jaar ga je met deelpensioen en ik hoop dat we samen nog veel leuke dingen kunnen ondernemen.

Lieve Titia en Michiel, ik ben heel trots op hoe jullie je ontwikkeld hebben tot maatschappijbewuste volwassenen en ben natuurlijk apetrots dat jullie paranimf willen zijn. Bedankt voor jullie belangstelling voor de voortgang van mijn onderzoek. Titia, bedankt voor jouw ondersteuning door alle figuren in het door de journals gewenste format om te zetten en voor de opmaak van het proefschrift. Ik was al zeer onder de indruk van de professionaliteit waarmee je de versie voor de leescommissie vorm hebt gegeven maar de opmaak van het proefschrift overtreft dit nog.

En last but not least Jan. We zijn al meer dan veertig jaar getrouwd en het leven is nog steeds een verrassing. Bedankt voor je ondersteuning in de afgelopen jaren. Het is best een intensieve periode geweest. Maar binnenkort hoef je bij de planning van leuke activiteiten geen rekening meer te houden met onderzoeksperiodes, schrijven, aanbieden en verwerken van commentaren van referenten en ook hoeft de pc niet meer mee op reis. Ik verheug me er op straks meer tijd te hebben voor leuke uitstapjes, afspraken, tennispartijtjes en misschien ook nog wat verre reizen. Ik hoop dat we nog lang mogen genieten van ons pensioen.

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List of publications and presentations

(Inter)national publications presented in this thesis

Lelie-van der Zande AC, Bouvy ML, Teichert AM. Patterns of recurring dispensing of guideline antibiotics for uncomplicated urinary tract infection in women over a 5-year period: Longitudinal patterns of recurring dispensings of Dutch guideline UTI antibiotics. *Family practice*. 2020.
<https://doi.org/10.1093/fampra/cmaa110>

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Rian Lelie-van der Zande, Ellen Koster, Martina Teichert and Marcel Bouvy. Barriers and facilitators for evidence-based self-care counselling in community pharmacy: Congresabstracts Prisma-symposium 19 mei 2022: 2022;7:a1759. Available from: <https://www.npfo.nl/artikel/prisma-symposium-19-mei-2022>

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Presentations

FIP Pharmacy Practice Research 2022

Barriers and Facilitators for Evidence-Based Self-care Counselling in Community Pharmacy

Gastcollege masteropleiding Utrecht 2020 en 2022

Zelfzorgadvies in de apotheek

KNMP Voorjaarscongres 2022 Lunchsessie

Zelfzorgadvies in de openbaar apotheek: versterkende en belemmerende factoren

Prisma symposium 2022:

Zelfzorgadvies in de openbaar apotheek: versterkende en belemmerende factoren (samenvatting gepubliceerd: Prisma-symposium, 19 mei 2022. Nederlands Platform voor Farmaceutisch Onderzoek 2022;7:a1759)

Prisma symposium 2021:

- Zelfzorgadvies voor allergische rhinitis: mystery shopping onderzoek
- Kennis van vrouwen met blaasontsteking over preventieve maatregelen
- Mening openbaar apothekers en huisartsen over zelfbehandeling blaasontsteking

Poster presentations

PCNE Working Conference

2020: Recurrence of acute cystitis in healthy non pregnant women: a longitudinal study with dispensing data in the Netherlands

2019: Treatment of uncomplicated urinary tract infection: a retrospective cohort study in women of 18 years and older using pharmacy dispensing data

Referent of manuscripts and subsidy applications

Referent for Exploratory Research in Clinical and Social Pharmacy, Plos One and ZonMw.

About the author

Rian Lelie-van der Zande was born in 1954 in Willemstad, the Netherlands. In 1972 she graduated from the St. Gertrudislyceum, Gymnasium β in Roosendaal. She obtained her pharmacy degree in Leiden in 1980. After graduation, she started working at the KNMP Medicines Information Centre. She became editor-in-chief of the *Informatorium Medicamentorum*. She developed self-care guidelines (zelfzorgstandaarden) and implemented them, both in community pharmacies and in the education of pharmacy assistants and the university curriculum. From 1996 until 2017 she was manager of the Medicines Information Centre. In this period, with her team she developed innovative products for supporting pharmacists and prescribers such as dosage advice for reduced kidney function, pharmacogenetics and obesity, advice for drugs and driving and *apotheek.nl*, thereby providing medicines information for patients and consumers. She also worked on exchange of contra-indications, allergies and lab results between healthcare providers, both on standardisation of data and on policy. With the GP organisation NHG and community pharmacists and GPs from practice she developed LESA's to improve patient care by agreements between the healthcare providers. She was chair of the advisory board of EPHOR (expertise centre pharmacotherapy for the elderly), and a member of the ZonMw program committee antibiotic resistance, of the CBG committee for practice, and of the executive committee of the FIP Health and Medicines Information Section. In 2017 she started her PhD as an external PhD student at the Division of Pharmacoepidemiology and Clinical Pharmacology. During her PhD project she was a member of the expert panel of AMP Onderzoek & advies in de zorg and member of the advisory group of the Zinnige Zorg Verdiepingsonderzoek Urineweginfecties at Zorginstituut Nederland.

In 2020 she reached retirement age but continued working on her PhD studies. She lives in The Hague, is married and has a daughter and a son.

