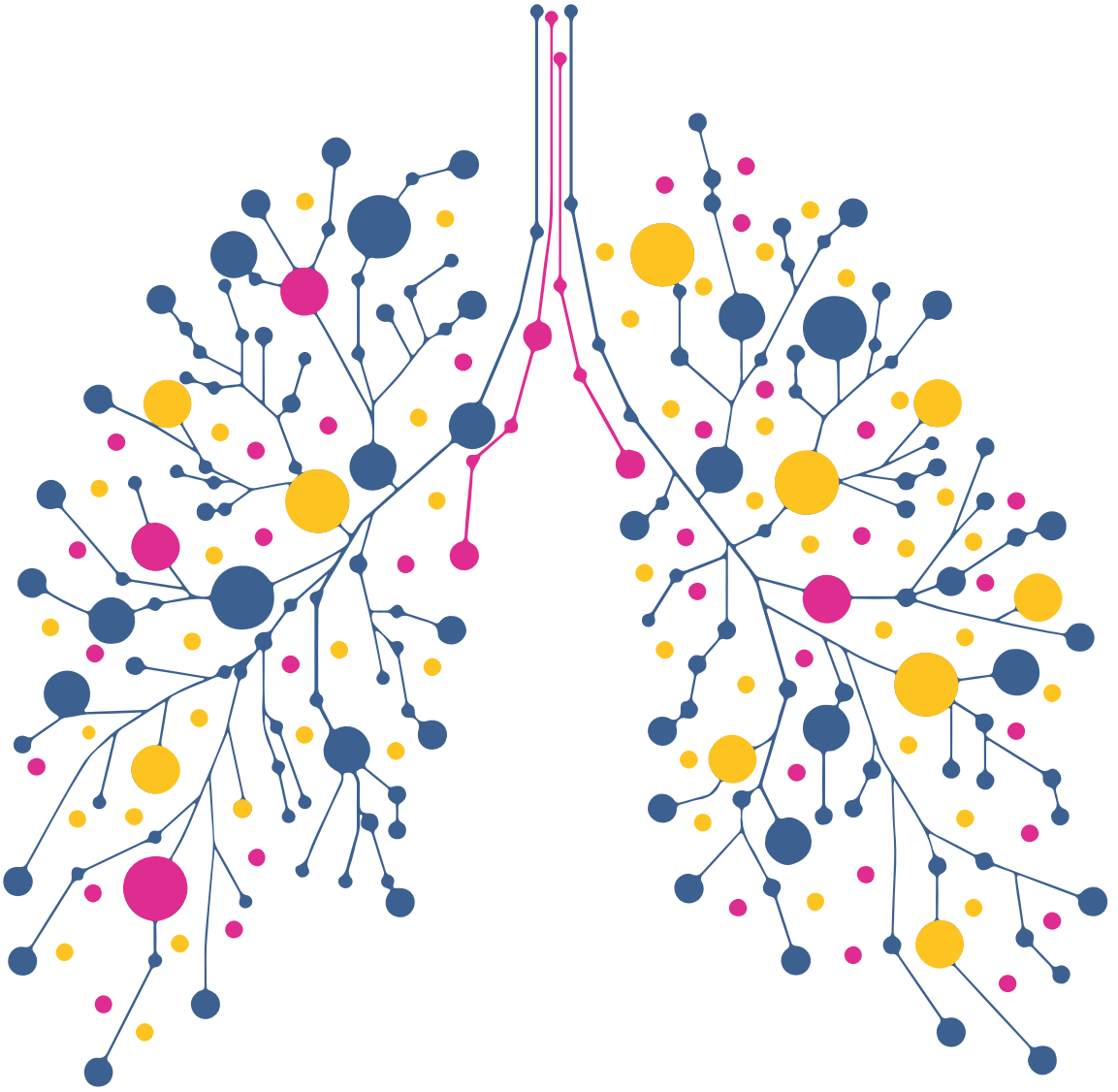
# Pharmaceutical care in obstructive lung diseases: current and future practice



Esther Kuipers

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The studies presented in this thesis have been performed at the Scientific Center for Quality of Healthcare (IQ Healthcare). This center is part of the Radboud Institute for Health Sciences (RIHS), one of the approved research institutes of the Radboud University Medical Center.

For reasons of consistency within this thesis, some terms and section orders have been standardized throughout the text. As a consequence, the text may differ in this respect from the articles that have been published.

The studies in this thesis were financially supported by the Royal Dutch Pharmacists Association (KNMP) and AstraZeneca Nederland. Financial support by the Department of Clinical Pharmacy of the Radboud University Medical Center, the Dutch Foundation for Asthma Prevention, and Stichting KNMP Fondsen for the publication of this thesis is gratefully acknowledged.

ISBN/EAN: 978-94-6375-632-7

Cover design by Birgit Vredenburg
Layout and design by Birgit Vredenburg, persoonlijkproefschrift.nl.
Printing: Ridderprint BV | www.ridderprint.nl

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**Pharmaceutical care in obstructive lung diseases:**

**current and future practice**

Proefschrift

ter verkrijging van de graad van doctor

aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,

volgens besluit van het college van decanen

in het openbaar te verdedigen op donderdag 20 februari 2020

om 14:30 uur precies

door

Esther Kuipers

geboren op 9 mei 1986

te 's-Hertogenbosch

| | |
|---|---|
| Promotoren: | Prof. dr. P.A.G.M. de Smet |
| | Prof. dr. M.J.P. Wensing |
| Copromotor: | Dr. M. Teichert |
| Manuscriptcommissie: | Prof. dr. A.M. van Dulmen |
| | Prof. dr. W.J.J. Assendelft |
| | Prof. dr. ir. C.E.M.J. van Dijk (RUG) |

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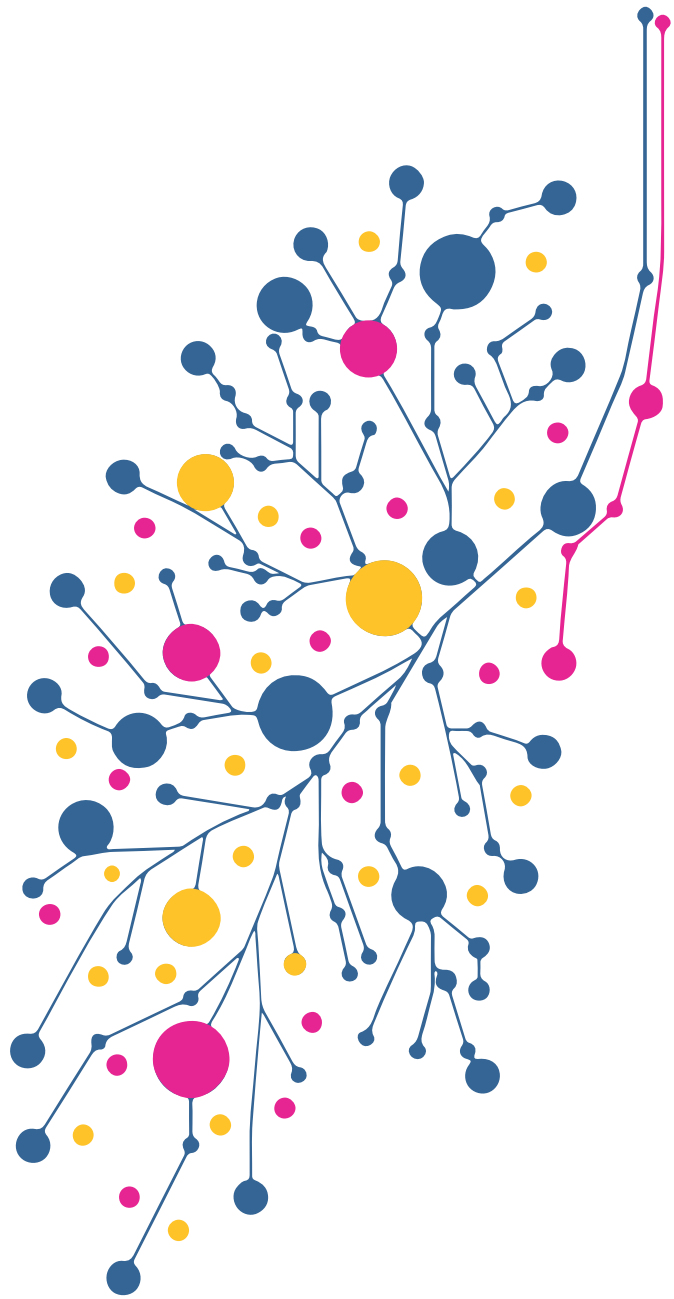
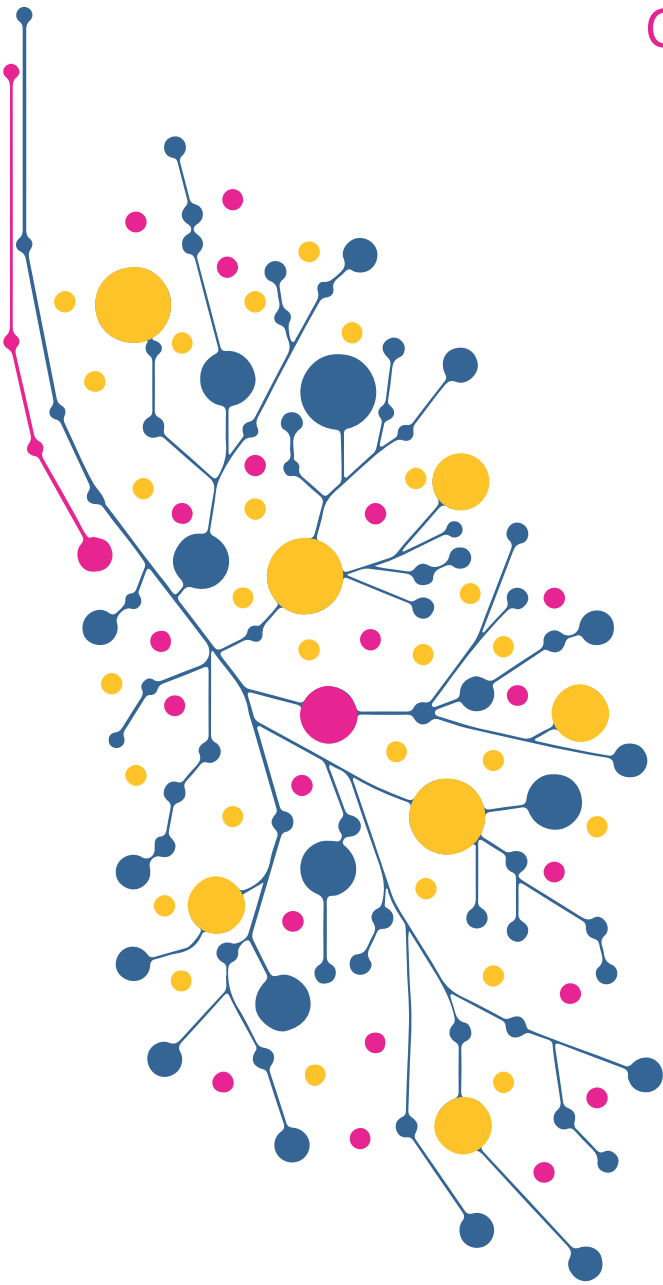


# Chapter 1

## General introduction



# General Introduction

## Pharmaceutical care

Community pharmacy practice was subject to immense changes in the last decades; the profession of community pharmacists has extended the traditional role of medication dispensing towards the provision of patient-centred pharmaceutical care (1-5). Pharmaceutical care is a broad concept, which has continued to evolve over the years with many different definitions appearing in the literature. Pharmaceutical care is stated to be "the pharmacist's contribution to the care of individuals in order to optimise medicines use and improve health outcomes" (6). As there is a need for standardisation of care that reflects the best available evidence to guide practice, guidelines have been developed according to the principles of evidence-based medicine (EBM) (7, 8). EBM has been defined as "the integration of best research evidence with clinical expertise and patient values" (9). Several pharmacy practice guidelines have been developed, in order to describe optimal pharmaceutical care for specific patient groups, reduce unwanted practice variation and ultimately improve the quality of healthcare (10-12).

## Pharmaceutical care in obstructive lung diseases

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases, affecting an estimated number of 641.000 and 600.000 people respectively in the Netherlands (13, 14). Although these diseases differ fundamentally, the treatment goals are fairly similar, aiming to minimize the risk of an exacerbation, control respiratory symptoms and maintain activities in daily life (15, 16). The first line administration method in the management of lung diseases is the inhaled route, and many factors affect the success of therapy; for example medication adherence and the ability to use the medication properly (17-19). There are many different types of inhaler devices available, which can differ in terms of the type of formulation (e.g. dry powder or solution), the way of dose preparation, single- or multidose devices, and the way in which the inhaler dispenses the medication (active or passive generation of the dose) (19). Several studies have demonstrated that many patients fail to handle their inhaler device correctly (17, 20-22), although patients are often not aware and overestimate their own abilities (23). Consequences of inadequate inhaler technique include a decrease in medication efficacy, because of a decreased deposition of medication in the lungs (19).

At present, the pharmacist's role in asthma and COPD treatment mainly includes handling computerized medication surveillance signals, giving inhalation instruction, and providing patients with information on disease and medication during dispensing visits (24). Several studies have shown that pharmaceutical care interventions, focusing on patient education and inhaler technique, have the potential to improve medication adherence and health outcomes (24-29). However, although the number of guidelines is increasing, pharmacists are challenged to grow in applying a patient-tailored approach in daily practice and adapt the provided pharmaceutical care to the individual patient's needs (30-32). For example, the pharmacists may provide tailored counselling regarding medication adherence and inhaler use technique, smoking cessation, and referring to the general practitioner (GP) when there

are signs of worsening disease control (24). Good communication skills of pharmacists are important in encouraging active patient participation, which is likely to be associated with positive health outcomes (33-35).

During the consultation of a healthcare professional, there are two needs that have to be met; 'the need to know' (to know and understand what is the matter) and 'the need to feel known' (to know that he/she is taken seriously and accepted) (36). Earlier studies have suggested that patients with chronic diseases are receptive for pharmacist counselling regarding newly started medications and that providing patients with appropriate, tailored information has potential to improve their behaviour, like medication adherence (37-39). Although the clinical importance for the use of inhaled corticosteroids (ICS) is different for asthma and COPD, ICS are currently prescribed as anti-inflammatory maintenance therapy for regular use in both conditions. As community pharmacists have an important role in supporting patients to use their medication optimally, they discuss the medication adherence independent of the underlying disease.



Newer technologies, like eHealth applications, are increasingly important in chronic diseases and have been studied for many years (40, 41). In addition to the available evidence-based guidelines, these technologies can offer pharmacists possibilities for providing more patient-tailored interventions. For example, there are electronic inhalation monitoring devices (EIMDs) available that measure inhalation actuations and provide detailed data on patient adherence to treatment to both patient and healthcare providers (41-44). Using an EIMD with audio-visual reminders and feedback has been demonstrated to have the potential to increase adherence to preventive medication, by facilitating self-management and clinical decision making (45-51). Self-management is shown to be effective in improving outcomes in patients with asthma, and this evidence is increasing for patients with COPD (52). However, EIMDs are not yet applied regularly in daily practice and the knowledge on pharmacists' and patients' experiences is limited.

## Outline of this thesis

In this thesis we focus on improving the insight into the current status and future possibilities of pharmaceutical care by Dutch community pharmacists in patients with obstructive lung diseases. This thesis consists of two parts.

In **part 1** we investigated the current status of pharmaceutical care in lung diseases. We performed a study on the actual performance of community pharmacists regarding recommendations from the professional asthma guideline for different pharmaceutical encounters (chapter 2). Second, we conducted a study on the use of non-selective β-blockers by patients with lung diseases (chapter 3). Chapter 4 describes a study on pharmacists' barriers and facilitators to participate in pharmacy practice research.

**Part 2** presents examples of advanced care in patients with lung diseases and provides insights into possibilities for future practice. Chapter 5 describes a study regarding telephonic counselling shortly after the start with inhalation maintenance therapy. We

also studied the effects of tailored pharmacists' interventions on patients' asthma control and medication adherence by prospective monitoring and the effects of an electronic adherence monitor- and reminder device on these outcomes (chapter 6). In chapter 7 we focused on the validity, usability and acceptability of this monitoring device for patient care as well as for objective measurement of medication adherence in research settings.

Finally, the results of these studies are summarised, discussed and put into a broader perspective in chapter 8.

*Research questions to be answered:*

1. What is the actual performance of community pharmacists regarding recommendations for different pharmaceutical encounters from the concept asthma care guideline?

2. Why are non-selective β-blockers prescribed and dispensed in patients with asthma and COPD?

3. What are community pharmacists' barriers and facilitators in considering participation in pharmacy practice research in the Netherlands?

4. What do patients want to share 2-3 weeks after starting with inhalation maintenance medication, regarding their symptoms, medication use, and other disease- and treatment related questions?

5. What are the effects of tailored pharmacists' interventions on patients' asthma control by prospective monitoring with patient-reported CARAT scores compared with a control group receiving usual care? What are the effects on ICS adherence and, the number of exacerbations and the use of an electronic adherence monitor- and reminder device?

6. What is the validity and the patient-reported usability and acceptability of an electronic adherence monitor- and reminder device in daily patient care and in clinical research?

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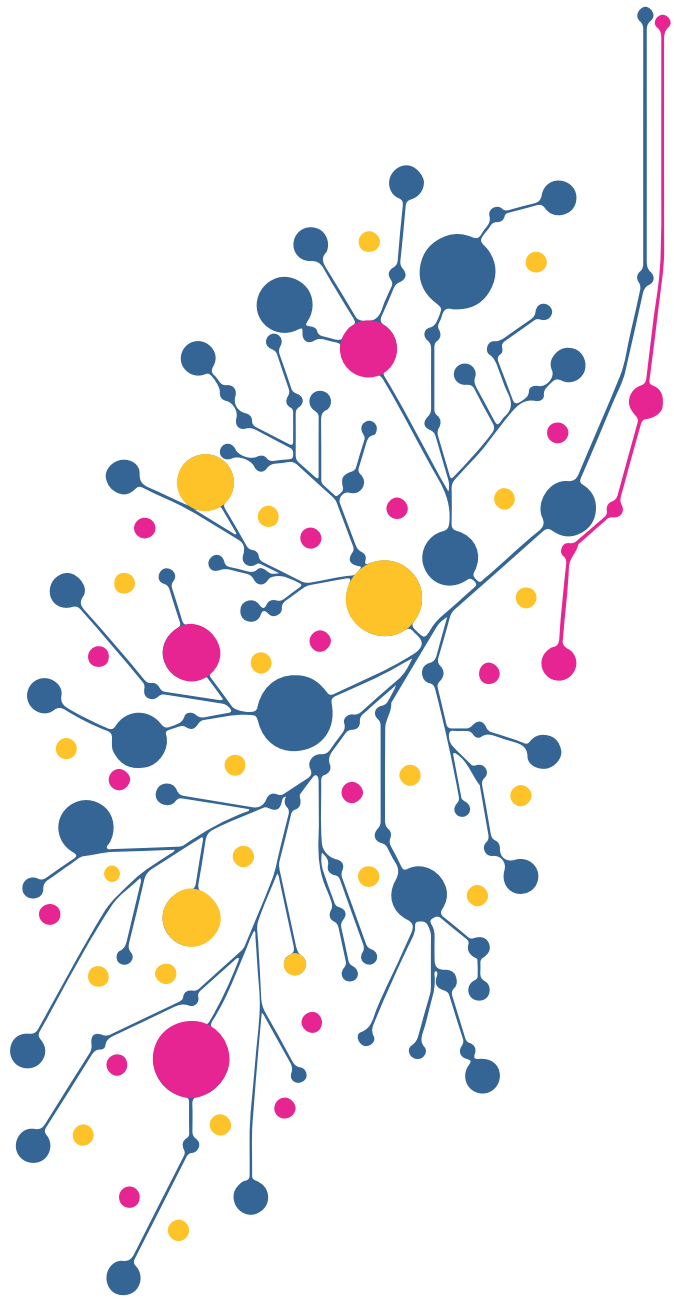
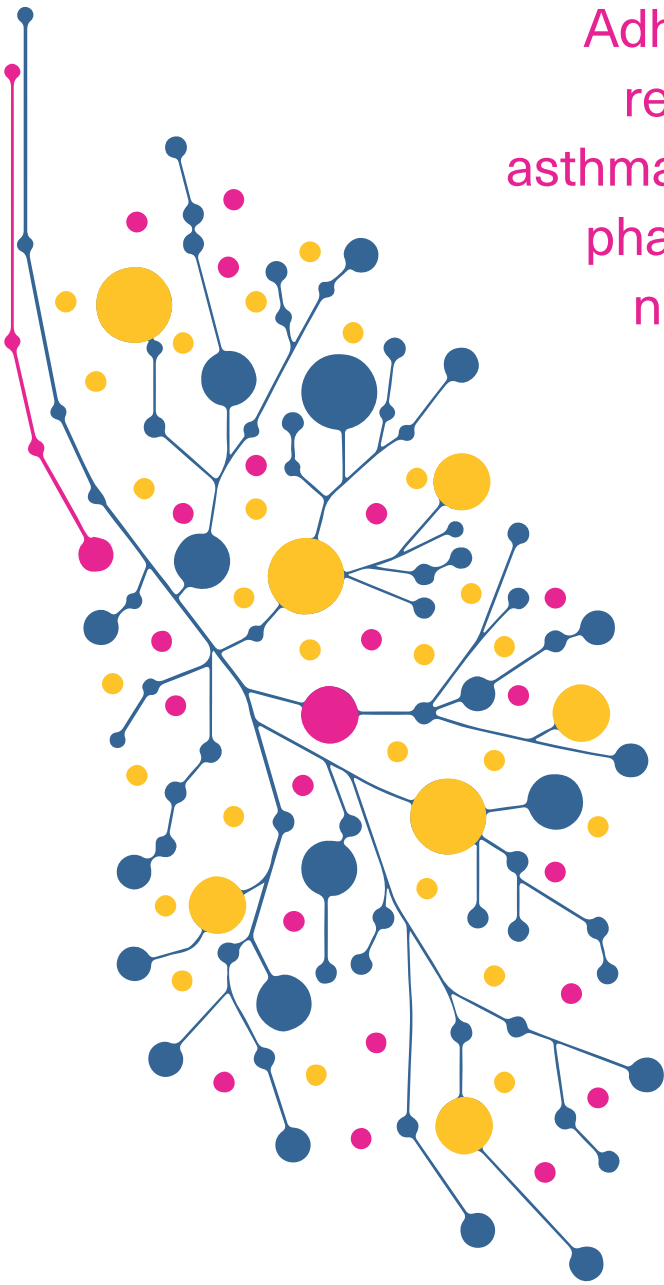


# Chapter 2

## Adherence to guideline recommendations for asthma care in community pharmacies: actual and needed performance



Esther Kuipers, Michel Wensing, Elaine Wong-Go, Bernard JG Daemen, Peter AGM De Smet, Martina Teichert

*NPJ Prim Care Respir Med. 2019 Jul 11;29(1):26*

# Abstract

## Background

Pharmaceutical care guidelines aim to provide recommendations for pharmaceutical care, reduce unwanted pharmacy practice variation and ultimately improve the quality of healthcare.

## Objectives

This study evaluated community pharmacists' adherence to recommendations for the provision of care to asthma patients with first dispensing and follow-up refill encounters in The Netherlands.

## Methods

Data were pharmacists' self-assessment of adherence to guideline recommendations, independent observations of dispensing encounters, and a nationwide questionnaire on pharmacists' views on the desirable (clinical) necessity of applying guideline recommendations to their patient population.

## Results

The 21 pharmacists who performed self-assessment judged their adherence concerning inhalation instructions as high. The lowest scores were reported for recommendations to collect additional information on the type of lung disease and for asking patients' expectations, wishes and concerns. Sixty-eight dispensing encounters were observed. In 83% of the 35 first dispensing observations, inhalation instruction was provided. This percentage was lower (62%) at refill dispensings. During all encounters, pharmacy staff seldom explored patients' perceptions or responded to patients' expectations, wishes and concerns. One hundred and four pharmacists completed the feasibility questionnaire. Pharmacists judged that all patients should receive inhalation instruction at first dispensing. They regarded it necessary to check on patients' expectations, wishes and concerns regarding the treatment for only up to 70% of the patients.

## Conclusion

More efforts on guideline implementation are needed, especially on follow-up dispensings and on gaining relevant information from patients and other healthcare professionals. Pharmacists still have opportunities to grow in applying a patient-tailored approach and exploring patients' individual needs, rather than providing practical information.

# Introduction

Pharmaceutical care guidelines aim to describe optimal pharmaceutical care (i.e. timely and appropriate patient-centred care, tailored to the individual patient's needs), the care patients and stakeholders can expect from pharmacists and ultimately improve the quality of healthcare, by providing pharmacists with recommendations that reflect prevailing knowledge (1, 2). The Royal Dutch Association for the Advancement of Pharmacy (KNMP) has recently developed a new guideline for asthma care (3). The guideline recommendations address pharmacotherapy in asthma, multidisciplinary cooperation with other healthcare professionals (e.g. general practitioners (GPs) and lung specialists), the dispensing process, patient monitoring and counselling. By providing pharmaceutical care to patients with asthma, the pharmacist can help them to achieve treatment goals, e.g. improvement of disease control and reduction of asthma symptoms, exacerbations and medication-related side effects (4-10). The pharmacists and their team have an important role in medication counselling, especially at the encounters during the dispensing moments in daily practice. They have good opportunities to inform and counsel patients and support them in using their medication properly (11-14). After treatment initiation with a pharmaceutical encounter during the first dispensing (FD) of asthma maintenance medication, patients return to the pharmacy for the first refill (second dispensing, SD), followed by general refill dispensings (RDs). The guideline contains 23 recommendations for pharmaceutical encounters (14 for FDs, 7 for SDs and 2 for RDs) and emphasises the importance of patient counselling. Especially, information on in using the inhaler correctly is essential, because incorrect inhaler technique and non-adherence to therapy are recognised as major factors in poorly controlled or uncontrolled asthma (15-17). The information during the FD is targeted to the starting patient, focusing on the inhalation instruction, tailored information to encourage good drug use and the appropriateness of the inhaler for the individual patient. The guideline recommendations regarding SDs focus on patients' first experiences with the medication (e.g. inhalation technique, effect, side effects).



The period between the first and the second prescription is decisive for the start and subsequent adherence to the medication scheme (11-14). During the consultation of a healthcare professional, there are two needs that have to be met: 'the need to understand (to know and understand what is the matter) and 'the need to be understood' (to know that he/she is taken seriously and accepted) (18). To meet both pharmacists' and patients' needs, the pharmacist should alternate information-giving and information-asking during patient encounters (18). Regarding pharmaceutical encounters in general, the guideline states that these are ideally based on reciprocal trust and shared decision-making, according to the Calgary-Cambridge model (19, 20). Good communicative skills of pharmacists can encourage active patient participation, which is likely to be associated with positive health outcomes (21-23).

However, an effect on clinical practice only can be attained by successful implementation of the guideline recommendations into daily routines (24-26). There are several success factors and barriers that may enhance or impede the implementation of the recommendations in

daily practice (1, 24-30). The guideline development follows a standardized process and consecutively involves drafting the text based on the existing literature and expertise, early assessment in daily practice, asking experts and organisations for feedback, and accreditation and publication. Therefore, before guideline authorization, a practice test on the actual situation and assessment of the feasibility for implementation has to be performed. In previous studies, adherence to different asthma care guidelines was mainly assessed in surveys by self-assessment of the healthcare professionals (29, 31) or by retrospective extraction from patient records (32, 33). However, it is obvious that not all care-related activities are documented completely and uniformly, and studies have shown that observation in daily practice also can provide meaningful additional information (34, 35). Furthermore, it may not always be necessary or even wanted to apply the guideline recommendations to all patients individually. Thus, the expectation of finding complete follow-up of all guideline recommendations for the patient population cannot be met from a patient-centred approach. The estimation of healthcare providers on the scores for their population can help to achieve a realistic perspective on the feasibility of adherence to guideline recommendations in clinical practice.

In this study we aimed to assess the actual performance of community pharmacists regarding recommendations for different pharmaceutical encounters from the concept asthma care guideline, using (1) pharmacists' self-assessment, (2) real-time observations and (3) a questionnaire on the scores to be achieved on population level for guideline recommendations with regard to individual patient needs.

# Methods

## Ethical approval

The study protocol was approved by the Ethical Committee of the Radboud UMC Nijmegen (approval number: 2018-5057). We have complied with all relevant ethical regulations.

## Design

This observational study consisted of several elements: (1) pharmacists' self-assessment of adherence to guidelines, (2) real-time observations of adherence to guidelines in daily practice, and (3) a nationwide questionnaire on pharmacists' assessment of the necessity to follow the recommendations at a population level.

## Setting

A convenience sample of 21 community pharmacies in The Netherlands was available for the self-assessment and real-time observations. During their second year of master's education in the University of Leiden, 21 pharmacy students followed their internship in community pharmacies, under the supervision of practising pharmacists who were specialised in community pharmacy and were trained to supervise students. Before the start of their internship, the students were educated in asthma symptoms (e.g. shortness of breath, wheezing sound when exhaling), treatment and pharmaceutical care according

to the professional guideline. Additionally, they received a briefing and written instructions about their role of observers in the research project. All pharmacists verbally agreed to participate in this study, as part of a practical assignment during the internships.

Pharmaceutical care in community pharmacies in The Netherlands has been previously described in detail (13, 36). Because most patients in The Netherlands attend a single community pharmacy, pharmacists usually possess the complete medication histories of their patients (37, 38). Community pharmacists and GPs had regular structured pharmacotherapy audit meetings since 1990. In these local meetings, they make agreements on pharmacotherapy based on national guidelines to improve prescribing and dispensing of drugs (39, 40).

## Guideline recommendations

The researchers selected the 23 guideline recommendations for pharmaceutical encounters (14 for FDs, 7 for SDs and 2 for RDs) from the concept asthma guideline. Dispensings are defined as FD when there was no dispensing of the same medication in the year before. All further following dispensing encounters after SD were defined as RDs.



During the RDs, the guideline recommends discussing patients' experiences and possible problems, if necessary. After patients had been using the medications for a period of time, the pharmacist was advised to screen the patients on drug therapy related problems and suboptimal medication use (e.g. overuse of rescue mediation, underuse of maintenance medication, inappropriate inhaler use or non-adherence) during the encounters or by clinical decision support systems (41).

## Measures

For each of the 23 recommendations, the pharmacists answered the self-assessment questionnaire on a Likert scale with the options: 'we do this in 0-20% of the situations', 'we do this in 20-50% of the situations', 'we do this in 50-80% of the situations', and 'we do this in 80-100% of the situations'. Pharmacy characteristics (e.g. team size and the availability of a consulting room) were collected.

Each student performed real-time observations of pharmaceutical encounters by the pharmacy staff (both pharmacists and pharmacy assistants) in daily practice during the internship. They noted their observations using a standardised scoring list with 'yes' and 'no' options for each of the 23 selected recommendations. In addition, they were invited to reflect freely on their personal observations, answering the question "what did you notice in this encounter?" All students were educated on asthma symptoms, the medications and the guideline recommendations. They received additional training on the use of the checklists and instructions to observe at least two dispensing encounters in daily practice. They were independent observers and did not intervene.

All pharmacists in The Netherlands were invited to complete a questionnaire regarding the necessity to follow the 23 selected recommendations at population level. They were asked

to score the minimum level (%) of adherence for each recommendation. To determine this, pharmacists were asked to consider the need to apply certain recommendations (e.g. do all patients need inhalation instruction, do all patients need a repeated instruction) only as they pertain to individual patients and to assume that all organisational preconditions (e.g. time, incentives, skills of the pharmacy staff, computer support) were met. They answered questions 'for which minimum percentage of patients should this recommendation be ideally followed for optimal implementation of this guideline recommendation in clinical practice?' on a 10-point Likert scale with 10 categories: 0-10% of the patients, 11-20%, 21-30%, etc. An e-mail invitation to participate in the survey was sent to 1936 community pharmacies in The Netherlands. Non-responders were sent a reminder 1 week later. The questionnaire was distributed nationwide to give all pharmacists the opportunity to share their opinions, but pharmacists from the special interest group on lung diseases from the KNMP and the pharmacy practice network were specifically invited to complete the questionnaire. Together with the questionnaire, the respondents received an instruction to focus on the desirable (clinical) necessity for the patients and not on the practical (organisational) feasibility in the pharmacy.

### Data analysis

Data from the self-assessment and observations were documented in Microsoft Word 2010. Descriptive statistics were used. For the necessity questionnaire, we reported the upper value of the category as scored by the pharmacists. Depending on the type of variable, the measures of dispersion were analysed using median and IQR for non-normally distributed variables and mean and SD for the normally distributed variables. All analyses were performed using IBM Corp SPSS statistics, Chicago IL, USA, version 25.

## Results

### Basic pharmacy characteristics

All pharmacists from 21 community pharmacies reported that they worked according to a certified quality management system. Overall they reported that they cooperated well with GPs in structured pharmacotherapy audit meetings. A consulting room was available in all pharmacies. The mean team size was 1.71 (SD 0.83, range 0.85-3.4) fulltime equivalent (FTE) pharmacists, and 8.11 (SD 3.27, range 4-15) FTE pharmacy assistants.

### Self-assessment

Twenty-one pharmacists completed the self-reported adherence questionnaire on the implementation of the guideline recommendations regarding the three types of dispensing encounters. Regarding the FD encounters, for 5 out of 14 items, the majority (≥16 of the 21 pharmacists) reported to be 80%-100% adherent (Table 1). These included checking the appropriateness of the inhaler for the patient, checking if inhalation instruction already had been provided, giving inhalation instruction if necessary, using the protocols of the Lung Alliance Netherlands (LAN) for the instruction and making sure that all information was understood by the patient. Nine recommendations showed lower adherence rates, with the

lowest scores for verification of the type of lung disease; checking patients' expectations, wishes and concerns regarding the treatment; and making appointments for follow-up consultation or repeated inhalation instruction.

**Table 1.** Adherence to guideline recommendations from pharmacists' self-report, independent observations and reported necessity for adherence

| **Recommendations for first dispensing** | **Self-reported adherence** (frequency)[1] We do this in ....% of the situations) | | | | **Observed adherence** [2] [% of the encounters] | **Necessary adherence** [3] for patient population [%], (IQR))[4] |
|---|---|---|---|---|---|---|
| | 0-20% | 20-50% | 50-80% | 80-100% | | |
| Check whether the inhaler is appropriate for the patient | 1 | 1 | 3 | 16 | 68.6 | 90 (72.5-100) |
| Use the LAN protocols for inhalation instruction | - | - | 5 | 16 | 91.4 | 90 (80-100) |
| Check if the patient has already received inhalation instruction from another healthcare provider | - | - | 4 | 17 | 68.6 | 90 (80-100) |
| Give inhalation instruction (or make sure that another healthcare provider did, dependent on local agreements) | 1 | - | 1 | 19 | 82.9 | 100 (90-100) |
| Verify the type of lung disease with the patient | 10 | 6 | 3 | 2 | 48.6 | 80 (60-90) |
| Check patients' expectations, wishes and concerns regarding the treatment | 8 | 6 | 4 | 3 | 22.9 | 70 (50-80) |
| Check what the patient already knows about asthma and the treatment | 4 | 7 | 6 | 4 | 40.0 | 70 (60-80) |
| Check what the patient already knows about the prescribed medicine | - | 5 | 6 | 10 | 68.6 | 80 (70-90) |
| Provide tailored advice focused on patients' individual needs | 1 | 3 | 6 | 11 | 62.9 | 80 (70-97.5) |
| Agree with the patient on subsequent counselling with inhalation instruction | 11 | 5 | 3 | 2 | 2.9 | 70 (50-87.5) |
| Check whether the patient understood the information | - | 1 | 3 | 17 | 97.1 | 90 (80-100) |
| Address service possibilities in the pharmacy (e.g. repeated prescription service, e-health, etc.) | 1 | 5 | 7 | 8 | 28.6 | 70 (50-80) |

**Table 1.** Continued

| **Recommendations for first dispensing** | **Self-reported adherence (frequency)**[1] We do this in ....% of the situations) | | | | **Observed adherence** [2] [% of the encounters] | **Necessary adherence** [3] for patient population [%], (IQR))[4] |
|---|---|---|---|---|---|---|
| Make an appointment for follow-up consultation in the pharmacy | 13 | 5 | 2 | 1 | 2.9 | 70 (40-80) |
| Note all relevant findings and follow-up appointments (if appropriate) | 5 | 3 | 5 | 8 | 14.3 | 80 (60-100) |
| **Recommendations for second dispensing** | | | | | | |
| Discuss agreements from the first dispensing encounter (if appropriate) | 8 | 9 | 2 | 2 | 46.2 | 70 (52.5-90) |
| Ask patient's experiences with the medication and possible problems | 2 | 5 | 5 | 9 | 100.0 | 80 (70-97.5) |
| Check patients' expectations, wishes and concerns regarding the treatment | 10 | 6 | 4 | 1 | 15.4 | 70 (60-80) |
| Check the inhalation technique and repeat the instruction if necessary | 2 | 8 | 5 | 6 | 61.5 | 80 (60-100) |
| Check whether it is needed to discuss topics that were unclear during the first dispensing or in need of repetition | 6 | 8 | 5 | 2 | 30.8 | 70 (52.5-80) |
| Check whether the patient understood the information | - | 1 | 8 | 12 | 84.6 | 90 (70-100) |
| Pay attention to the possibilities for follow-up consultation | 9 | 4 | 4 | 4 | 15.4 | 70 (50-80) |
| **Recommendations for follow-up dispensing** | | | | | | |
| Ask patient's experiences with the medication and possible problems | 9 | 8 | 2 | 2 | 40.0 | 70 (60-90) |
| Actively screen for suboptimal use of inhalation medication (e.g. overuse of SABA or medication non-adherence) | 4 | 5 | 3 | 9 | 25.0 | 80 (60-90) |

[1] n=21

[2] n=35 for FD, n=13 for SD, n=20 for RD

[3] n=104

[4] IQR: Interquartile range (quartile 1-quartile 3)

During the SD encounters, the highest score was found for checking whether the patient had understood the information. The lowest scores were reported for checking patients' expectations, wishes and concerns regarding the treatment and discussing agreements from the FD encounter (10 and 8 pharmacists do this in 0-20% of the situations, respectively).

Regarding the RD encounters, 17 out of the 21 pharmacists reported that they check patients' medication experiences in <50% of the situations.

## Real-time observations

Sixty-eight individual pharmaceutical encounters were observed: 35 FD, 13 SD, and 20 RD encounters (Table 1). For 3 out of the 14 items regarding the 35 FD encounters, the observed adherence rate was at least 80%. This included providing inhalation instruction (83%), using the LAN protocols for the instruction (91%) and, at the end of the counselling making sure that all information was understood by the patient (97%). For 4 items, the adherence rates were between 60% and 70%, including checking the appropriateness of the inhaler, assessing whether the patient had already received inhalation instruction from another healthcare provider, checking what was known about the prescribed medication, and providing tailored advice. The lowest adherence rates (3%) were found for the recommendations on appointments for a SD consultation for repeating the inhalation instruction. Checking patients' expectations, needs and concerns regarding the treatment (23%), and documenting all relevant findings and follow-up appointments (14%) were also not common during the FD observations. During the SD encounters, adherence rates remained low (15%) with respect to these two recommendations. Patients' experiences and possible problems were always (100%) discussed in SD encounters and in 40% of the RD encounters. During the RD encounters active screening on suboptimal use of inhalation medication (e.g. overuse of short-acting beta agonist or maintenance medication nonadherence) was observed in 25% of the follow-up refill encounters.

## Necessity questionnaire for adherence to guideline recommendations at the population level

One hundred and four expert pharmacists (response rate 5.4%) completed the questionnaire regard ing the expected necessity of adherence to the 23 recommendations at the population level regarding the needs of individual patients in daily practice (Table 1). The highest scores (adherence up to 90%) were reported on the recommendations regarding checking the appropriateness of the inhaler, using the LAN protocols, giving inhalation instruction and checking whether the patient understood the information.

The highest rate of consensus was for providing inhalation instruction. The lowest rate of consensus was for the FD recommendations regarding appointments for follow-up consultations (median score 70%, interquartile range (IQR) 40-80) and documenting the relevant findings (median score 80%, IQR 60-100); and for the SD encounters for checking the inhalation technique (median score 80%, IQR 60-100) and discussing agreements from the first dispensing encounter (median score 70%, IQR 52.5-90).

Overall, for 3 out of the 23 recommendations, the performance observed in daily practice reached the desired score. First, using the LAN protocols, was observed in 91.4% of the FD encounters (necessity score of 90%). Second, checking whether the patient has understood the information was reported to be necessary for at least 90% of the patients, and this observed in 97.1% of the FD encounters. Patient's experiences with the medication and

possible problems were asked in 100% of the SD encounters (necessity score of 80%). However, the pharmacists seemed to have underestimated their performance; the self-reported adherence was lower for these recommendations.

The largest differences in observed adherence and desired scores were found for the following recommendations: making an appointment for follow-up consultation in the pharmacy (2.9% observed vs 70% desired); agreeing with the patient on subsequent counselling with inhalation instruction (2.9% vs. 70%); noting all relevant findings and follow-up appointments (14.3% vs. 80%); checking patients' expectations, wishes and concerns regarding the treatment (15.4% vs. 70%); and paying attention to the possibilities for follow up consultation (15.4% vs. 70%).

## Discussion

This study provided insights in the actual situation and assessment of the feasibility of implementing recommendations from the concept asthma care guideline for community pharmacies in daily practice.

Overall, adherence to the guidelines varied across recommendations as well as pharmacists. There were similarities but also differences between the self-reported adherence, real-time observations and desired scores. This study showed that pharmacy staff members were focused on providing relevant information during the FD encounters, but the information was less comprehensive during RDs. First refills were not always recognized and acted upon, and when there were no appointments made after the FD, patients were possibly not aware of the opportunity for additional care activities.

To fulfil pharmacists' and patients' needs, the roles of information-giving and information-seeking have to be alternated during encounters. However, pharmacy assistants rarely explored patients' perceptions or asked about expectations, wishes and concerns. This has also been shown in earlier studies; pharmacy staff in community pharmacies generally provided practical information and seldom discussed patient's preferences and perceptions about prescribed medications (11, 14). Specifically, the topics for repeated dispensings were rarely discussed and the pharmacy staff members did not stimulate patients to ask questions, which is also found in other studies (14, 21, 42-45). In addition, the observers mentioned that although in the majority of the encounters pharmacists checked whether the patient had understood the information, this was asked in a rhetorical way rather than with an open question.

The results of the self-assessment and observations were added to by our questionnaire survey. In general, there was a lack of consensus among pharmacists. Clearly, there are some recommendations that should be followed for the large majority of the patients, for example, providing inhalation instruction or checking whether patients had understood all information and the appropriateness of the prescribed inhaler. However, pharmacists

reported lower feasibility scores for the majority of recommendations. Some of these recommendations (e.g. making appointments for follow-up consultations or addressing service possibilities) could be considered as optional, dependent on patients' needs. To improve patient outcomes, it is important to apply such a patient-tailored approach and adapt the provided care to the needs of the individual patient (15, 46, 47). Earlier studies have shown that patients with chronic conditions have a need and a desire for pharmacist counselling about new medications and that providing patients with appropriate, tailored information has the potential to improve medication adherence (48-50). However, to apply a patient-tailored approach, it should be even more important to recognize those needs in daily practice.

In this study, pharmacists reported in the questionnaire that checking patients' expectations, wishes and concerns regarding the treatment was desirable in just 70% of the patients, but during the observations, the score was much lower (22.9% for FD, 15.4% for SD). Apparently, pharmacists are still used to a protocol-driven way of providing information. However, to extend the traditional role of the pharmacist towards the provision of patient-centred pharmaceutical care, pharmacists should focus more on discussing patient's preferences, perceptions and needs rather than providing practical information. After all, it is difficult to provide patient-centred care when the type of lung disease (and consequently the guideline that should be applied) is not known or when patients' needs are not explored.



This study was a small scale assessment of adherence to guidelines in daily practice, combining observed practice and reported intention regarding the adherence of guideline recommendations. The independent observers considered the implementation of the guideline from a theoretical perspective, and the trained and educated pharmacists were experienced in working according guidelines in daily practice. This study was a first step towards evaluating guideline adherence and facilitating further research that explores barriers for poor adherence.

There are some limitations to our study. First, the self-assessment and observations were conducted in a small, convenience sample of 21 pharmacies; however, their characteristics did not differ from the national data (51). Second, the real-time observations were performed at single moments ('snapshots'), which may have led to bias. However, all pharmacists were experienced in pharmacy practice research and education, and were open to critical self-reflection. Third, the pharmacists were aware that they were being observed and thus the performances noted may have been better than normal performances. Consequently, the potential for improvement in clinical practice may be even higher for pharmacies in The Netherlands. Finally, because the feasibility questionnaire was not validated beforehand, some pharmacists might have experienced difficulty in comprehending the instruction or the language used.

## Conclusion

The guideline recommendations are formulated for the best quality of care to be provided from actual knowledge. With subsequent implementation of these recommendations, it is expected that pharmaceutical care will be improved. In conclusion, this study showed that, for a select group leading pharmacists, performance on information supply was high and performance in exploring individual patient's needs was low. More efforts on guideline implementation are needed, especially on follow-up dispensings and on gaining relevant information from patients and other healthcare professionals. These results indicate that more effort is needed to change the role of the pharmacist from a professional who dispenses practical information to that of a patient-tailored coach during medication use, according to the guideline recommendations. More research is needed to explore the barriers in clinical practice to change the behaviour of pharmacists and technicians.

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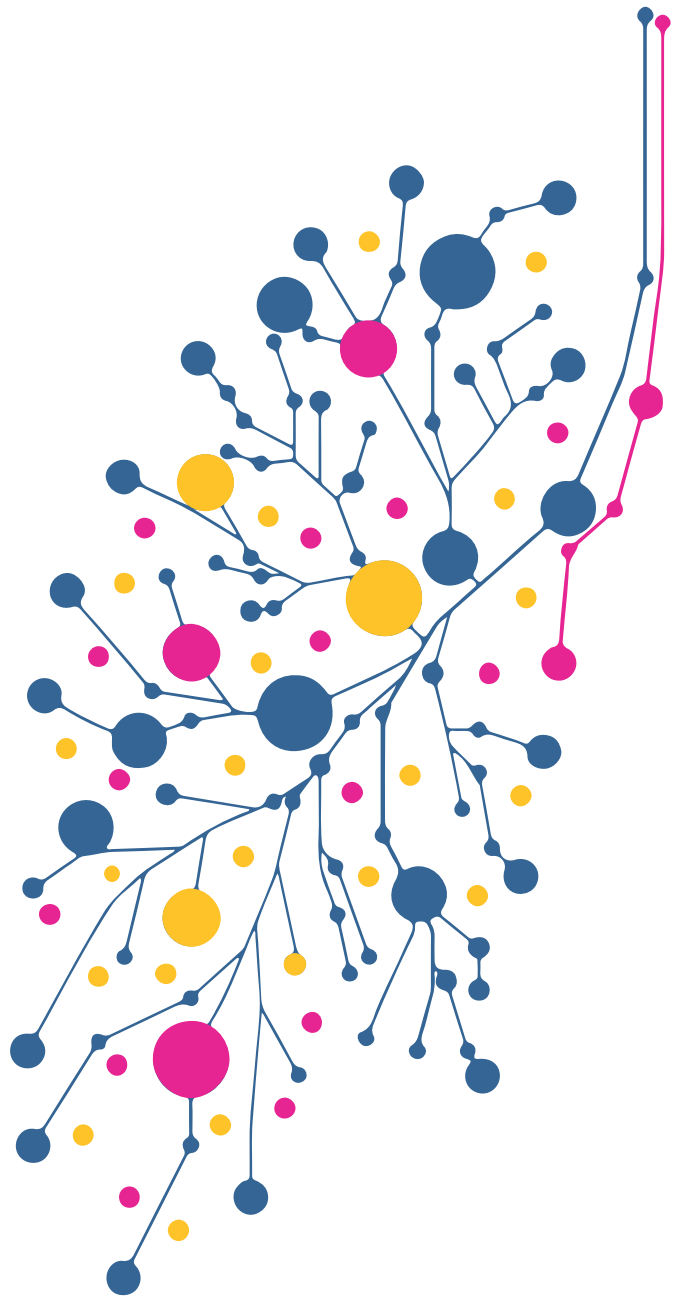
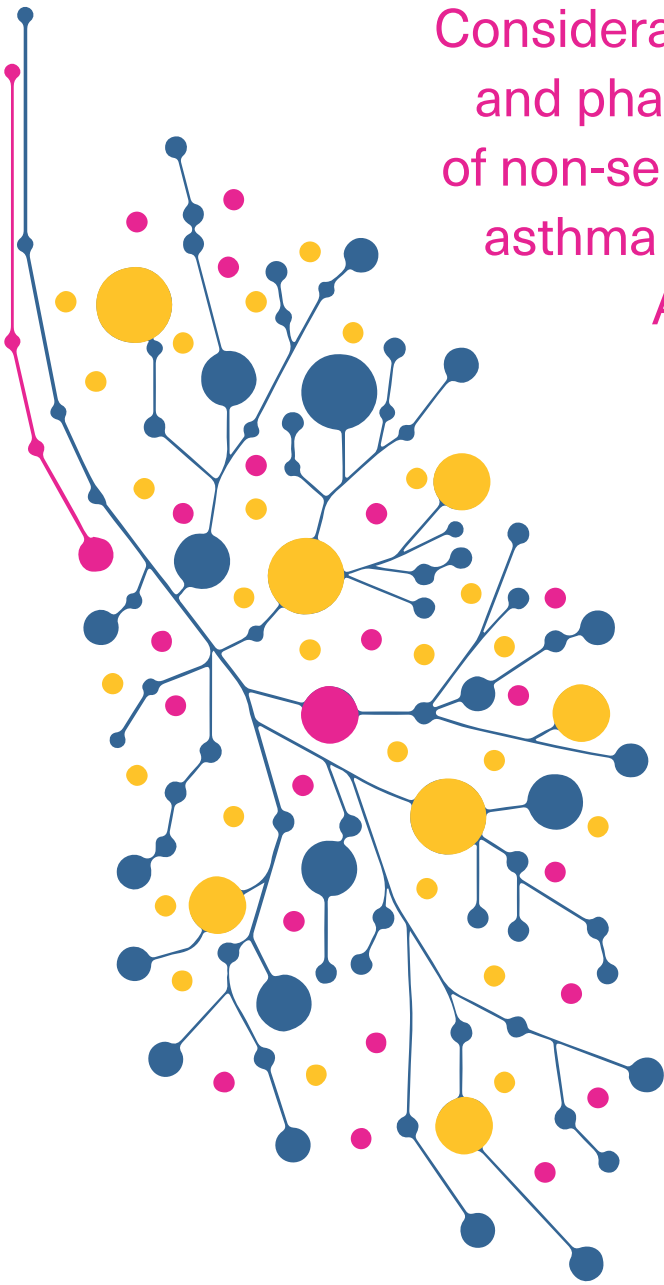


# Chapter 3

## Considerations of prescribers and pharmacists for the use of non-selective β-blockers in asthma and COPD patients: An explorative study



Esther Kuipers, Michel Wensing, Peter AGM de Smet, Martina Teichert

*J Eval Clin Pract. 2018 Apr;24(2):396-402*

# Abstract

## Rationale, aims, and objectives

Despite recommendations in prevailing guidelines to avoid the use of non-selective (NS) β-blockers in patients with asthma or COPD, on average, 10 patients per community pharmacy receive NS β-blockers monthly. The aim of our study was to identify the reasons of prescribers and pharmacists to treat asthma and COPD patients with NS β-blockers.

## Methods

Fifty-three community pharmacists in the Netherlands selected patients with actual concurrent use of inhalation medication and NS β-blockers. For at least 5 patients, each pharmacist screened all medication surveillance signals and actions taken at first dispensing. Each pharmacist selected 3 different initial prescribers for a short interview to explore their awareness of the co-morbidity and reasons to apply NS β-blockers.

## Results

Pharmacists identified 827 asthma/COPD patients with actual use of NS β-blockers. From these, 153 NS β-blocker prescribers were selected and interviewed (64 general practitioners, 45 ophthalmologists, 24 cardiologists, and 20 other prescribers). One hundred seven prescribers were aware of the drug-disease interaction of the asthma or COPD co-morbidity when initiating the NS β-blocker, and 46 were not. From these, 40 prescribers did not consider the contraindication to be relevant.

For 299 patients, medication surveillance signals and actions at first dispensing were retrieved. Patients used predominantly ocular timolol (39.8%), and the oral preparations propranolol (30.8%) and carvedilol (15.1%). In 154 cases, the pharmacy system generated a warning alert.

## Conclusions

A substantial number of prescribers was unaware of the co-morbidity or did not regard NS β-blockers contraindicated, despite prevailing clinical guidelines. Improvement programs should target prescribers' awareness and knowledge of NS β-blockers in patients with asthma or COPD.

# Introduction

Treatment with $\beta_2$-adrenoceptor agonists plays an important role in the treatment of asthma and chronic obstructive pulmonary disease (COPD). In patients with COPD, short-acting $\beta_2$-agonists (SABA) and long-acting $\beta_2$-agonists (LABA) are recommended to relieve airflow limitation (1, 2). In patients with asthma, SABA are used for acute relief of symptoms and LABA are used as add-ons to inhaled corticosteroids (ICS) for patients not achieving asthma control on therapy with ICS alone (3, 4).

$\beta_2$-Receptors are found in smooth muscle cells of the bronchi, whereas $\beta_1$-adrenoceptors are mainly located in the heart (1-4). Blocking $\beta_1$-receptors in the heart is essential in the treatment of several cardiovascular diseases, causing a reduction in heart rate and contraction force. Systemic treatment with β-blockers was shown to reduce mortality and the risk of arrhythmias and to delay heart failure after a myocardial infarction.5, 6 Ocular β-blockers are indicated for glaucoma and reduce the intraocular pressure by decreasing the production of aqueous humour (5, 7). Due to the potential risk of triggering bronchoconstriction and an insufficient response to bronchodilator therapy during an exacerbation, use of non-selective (NS) β-blockers in patients with asthma or COPD is contraindicated according to prevailing guidelines for lung diseases and glaucoma (1-4, 8).



Some β-blockers are selective antagonists at the β1-receptor (eg, atenolol, bisoprolol, and metoprolol), usually called “cardioselective” β-blockers. Other β-blockers (eg, propranolol and timolol) also show antagonist activity at β2-adrenoceptors; these drugs are referred to as “non-selective” β-blockers. Receptor selectivity of β-blockers is a dose-dependent property, as with increasing dose, the $\beta_1$-selectivity decreases (5, 9-11). Moreover, even in cardioselective β-blockers, β1-selectivity was shown to be relative (12), and these β-blockers can also cause $\beta_2$-mediated respiratory side effects as bronchospasm or a fall in forced expiratory volume in 1 second in susceptible individuals (5, 13-16). However, the contraindication in the guidelines is limited to NS β-blockers; fewer hospitalizations and emergency department visits occurred with cardioselective β-blockers, compared to NS β-blockers (5, 17-19). There was no convincing evidence for a clinically relevant influence of selective β-blockers on bronchoconstriction (1-5, 7, 15, 16, 20-25).

Despite this contraindication, on average, 10 users of inhalation medication per community pharmacy in the Netherlands were detected with NS β-blockers co-medication (26, 27) in 2016. From dispensing data only, it cannot be deduced whether or not the prescribing and dispensing of NS β-blockers for this population were due to deliberate clinical reasoning of prescribers and pharmacists.

Consequently, the primary objectives of this study were to assess whether prescribers were aware of the lung disease at the start of the NS β-blocker and, if so, to explore the reasons why these were prescribed. Furthermore, this study aimed to examine the way of signalling this drug-disease interaction in the pharmacy computer system and how the pharmacist dealt with this surveillance signals in daily practice.

# Methods

## Study design

This was an explorative observational study in 53 community pharmacies in the Netherlands. The study protocol was approved by the Ethical Committee of the Radboud UMC Nijmegen (approval number: 2015-2185).

## Setting

Fifty-three community pharmacists, located in different areas in the Netherlands, participated in this study between February and July 2016. These pharmacists belonged to 3 different educational groups within the national postgraduate specialization programme to become community pharmacists. Participating in research practice is part of the last year of this educational programme. Thus, the participating pharmacists were a convenience sample of all pharmacists in the Netherlands. Dutch pharmacists have a professional and legal responsibility for the drug treatment of their patients (28). All pharmacists in the Netherlands use a computer system, designed to signalize drug-drug interactions and, if applicable, intolerances and drug-disease interactions. Pharmacists use these signals to identify drug therapy-related problems and consult prescribers. Handling of all monitoring signals is registered in the local pharmacy system.

## Patient selection—identification

Patients were selected from pharmacy dispensing data. In the Netherlands, all medication dispensed on prescription is registered in the local pharmacy system. Dispensing data from more than 90% of the 1981 community pharmacies in the Netherlands are delivered routinely to the Foundation of Pharmaceutical Statistics (SFK). These data provide detailed information on the drugs dispensed, including the codes from the Anatomic Therapeutic Chemical (ATC) system of the World Health Organization (29). The computerized pharmacy system can only calculate correct periods of drug use, if the total number of dispensed drug doses and the prescribed daily dose is entered (30). From these data, SFK generates periodically online reports for participating pharmacies, to detect possible medication problems and to improve pharmaceutical care.

Participating pharmacists were provided with an automated web report that identified all users of inhalation medication for their pharmacy with actual use of NS (oral or ocular) β-blockers. The SFK web report presented all current users of inhalation medication for asthma or COPD (SABA, LABA, ICS or combinations of ICS/LABA, and short- and long-acting muscarinic antagonists; ATC code R03) that were also current users of an oral NS β-blocker (ATC codes C07AA, C07AG, C07BA, C07CA, C07DA, C07EA, and C07FA) or an ocular NS β-blocker (ATC codes: S01ED, except S01ED02 and S01ED52), independent of which medication had been started first.

### *Selection of NS β-blocker initiators for prescriber interview*

From the SFK web report, each pharmacist selected 3 prescribers from different disciplines for an interview about their choice to initiate the NS β-blocker for this population, based on a

semi-structured format (Appendix I). Pharmacists were asked to look for the first dispensing of an NS β-blocker in the patients dispensing history to identify the initial prescriber (initiator). A first dispensing was defined as the dispensing of an NS β-blocker without any dispensing of an NS β-blocker within the preceding 12 months. The first question in these interviews was whether the initiator was aware of the airway disease when starting the NS β-blocker. When this was the case, the pharmacist asked for the reasons to prescribe an NS β-blocker despite the drug-disease interaction and whether the choice would have been reconsidered if the patient would suffer from exacerbations after the start of the NS β-blocker. If the initiator was not aware, possible reasons for this were explored. Several possible reasons (eg, lack of a complete patient file and not interested in co-morbidities) were prepared in a digital form, with the possibility to add additional answers.

### *Selection of patients for occurrence and handling of surveillance signals*

From the web report, each pharmacist selected at least 5 current users of inhalation medication in combination with an NS β-blocker (aged 18 years or older). For each identified patient, all medication surveillance signals and actions taken at first dispensing were screened and the diagnosis of asthma or COPD and the reason for prescribing the oral NS β-blocker were verified with the general practitioner (GP), if possible. In daily practice, when patients are treated by different health care providers, lack of communication can lead to incomplete dossiers of all professionals involved. Moreover, diagnoses and reasons for drug prescribing are often not communicated to the community pharmacist. As an approach, the pharmacy information system can generate "deduced contraindication" signals from the medication dispensed. These can be judged by the pharmacist, verified by the prescriber, and stored in the system. For example, when a patient uses antidiabetic medication, the pharmacist can enter the contraindication "diabetes mellitus" into the pharmacy information system.

### Analysis

With descriptive analysis, answers were stratified for medical specialism (GP, cardiologist or ophthalmologist, pulmonologist, neurologists, psychiatrist, and other specialists) and awareness of the contraindication, and categorized for reasons that the NS β-blocker was prescribed in spite of the airway disease. Differences between prescribers were examined with the chi-square test, using IBM Corp SPSS statistics, Chicago IL, USA, version 22.

## Results

In 53 pharmacies, 827 patients were identified by the web report, dispensed NS β-blocker co-medication concomitantly with inhalation therapy for overlapping time periods. From this selection, medication surveillance signals were checked for 299 patients (Table 1) and 153 prescribers were interviewed.

**Table 1**. Characteristics of actual users of non-selective β-blockers together with inhalation medication (n=299)

| Parameter | |
|---|---|
| Male sex [n (%)] | 133 (44.5%) |
| Age [years; mean (SD)] | 69.52 (12.23) |
| **Lung disease [n (%)]** | |
| Asthma | 122 (40.8%) |
| COPD | 106 (35.5%) |
| Asthma/COPD combined | 51 (17.1%) |
| Other airway disease | 2 (0.7%) |
| Unknown | 18 (6.0%) |
| **NS-β-blocker [n (%)]** | |
| timolol ocular | 133 (39.8%) |
| levobunolol ocular | 1 (0.33%) |
| propranolol | 92 (30.8%) |
| carvedilol | 45 (15.1%) |
| sotalol | 15 (5.0%) |
| labetalol | 13 (4.3%) |
| **Indication NS-β-blocker [n (%)]** | |
| Glaucoma | 130 (43.5%) |
| Hypertension | 45 (15.1%) |
| Heart failure | 24 (8.0%) |
| Angina pectoris | 16 (5.4%) |
| Prophylaxis migraine | 15 (5.0%) |
| Atrial fibrillation | 4 (1.3%) |
| Anxiety | 4 (1.3%) |
| Tremor | 4 (1.3%) |
| Other indications | 7 (2.3%) |
| Unknown | 50 (16.7%) |

## Prescribers—interviews

A convenience sample of 153 NS β-blocker initiators (for 3 patients per pharmacy) was interviewed for this study. Sixty-four initiators were GPs, 45 were ophthalmologists, 24 cardiologists, and 20 other prescribers (e.g., neurologists, psychiatrists, and doctors of internal medicine).

One hundred seven initiators (69.9%) indicated to have been aware of the drug-disease interaction at the moment of prescribing the NS β-blocker (Figure 1). Reasons for choosing the NS β-blocker, despite the drug-disease interaction, are shown in Table 2. Of all initiators, 40 (37.4%) considered the co-morbidity asthma or COPD to be not relevant. Stratification for the different disciplines showed that 38.9% of the GPs, 63.6% of the ophthalmologists, and 35.7% of the interviewed cardiologists had this opinion ($P = .032$). During the interviews, ophthalmologists mentioned regularly to have never seen exacerbations in daily practice. Twenty-five initiators indicated a lack of alternative medication: 15 GPs (27.8%), 4 cardiologists (28.6%), 1 ophthalmologist (4.5%), and 5 of other disciplines (29.4%, $P = .139$).



**Figure 1.** Prescribers' awareness of asthma or chronic obstructive pulmonary disease co-morbidity at the moment of prescribing non-selective β-blockers

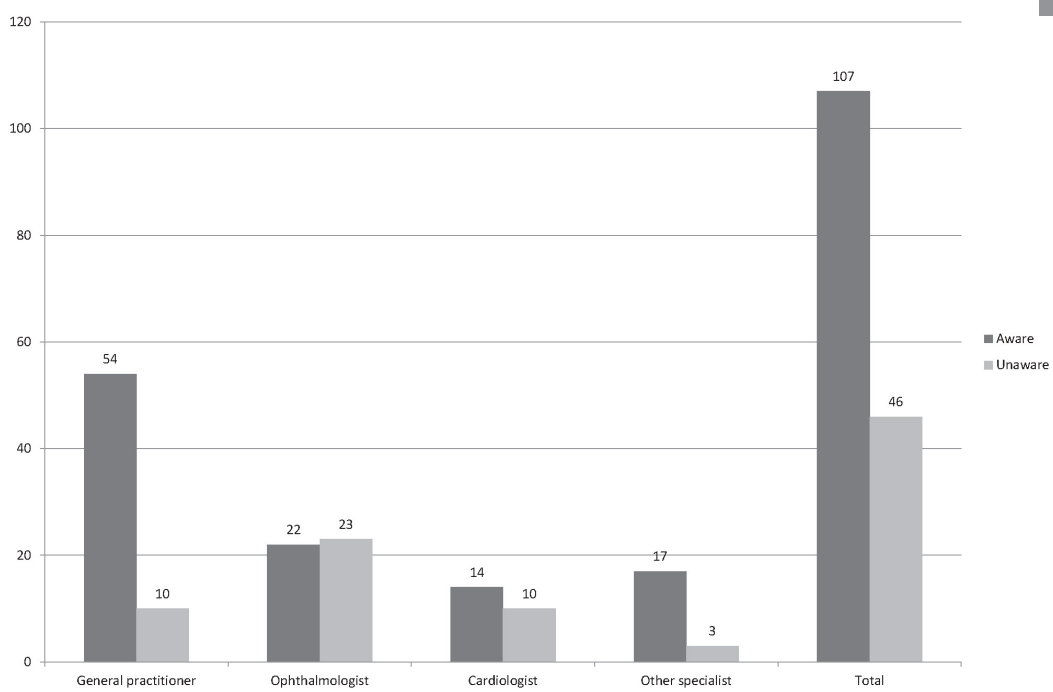


**Table 2.** Prescribers' reasons for choosing the non-selective β-blocker despite awareness of the contraindication

| Statements | GP* (n=54) | OP* (n=22) | CA* (n=14) | OS* (n=17) | Total (n=107) |
|---|---|---|---|---|---|
| Contra-indication not regarded to be relevant | 21 (38.9%) | 14 (63.6%) | 5 (35.7%) | - | 40 (37.4%) |
| Patient already tried alternative medication to NS-β-blocker | 10 (18.5%) | 6 (27.3%) | 4 (28.6%) | 3 (17.6%) | 23 (21.5%) |
| No alternative available for NS-β-blocker, β-blocker seemed the best option | 15 (27.8%) | 1 (4.5%) | 4 (28.6%) | 5 (29.4%) | 25 (23.4%) |
| Prescriber stated that there was no actual lung disease at start of the NS-β-blocker | 2 (3.7%) | - | - | 3 (17.6%) | 5 (4.7%) |
| No initiation, but repeating an earlier prescription of another prescriber | 4 (7.4%) | - | - | 1 (5.9%) | 5 (4.7%) |
| NS-β-blocker only for short term use | 2 (3.7%) | - | - | - | 2 (1.9%) |
| Other reasons | - | 1 (4.5%) | 1 (7.1%) | 5 (29.4%) | 7 (6.5%) |

*GP = general practitioner, OP = ophthalmologist, CA = cardiologist, OS = other specialist

Seventy-seven (72.0%) of the 107 prescribers would have reconsidered the use of the NS β-blocker when the patient had suffered from exacerbations after the start of the NS β-blocker. Stratification for the different disciplines showed 46 GPs (85%), 14 ophthalmologists (63.5%), 7 cardiologists (50%), and 10 other initiators (58.5%) that would prescribe alternative medication in case of an exacerbation ($P$ = .017).

Forty-six initiators (30.0%) mentioned not to have been aware of the lung disease when prescribing the NS β-blocker with the highest proportions in ophthalmologists (51.1%) and cardiologists (41.2%) and compared to GPs (15.6%, $P$ = .000). Most frequently mentioned reasons for this were incomplete patient records (n = 18) and the absence of asthma or COPD at the moment of prescription (n = 18). Four doctors (2 cardiologists and 2 ophthalmologists) declared that the lung disease was not part of their specialism. Fifteen of the 46 initiators (32.6%) declared that they would have chosen an alternative medication if they had been aware of the drug-disease interaction.

## Surveillance signals in the community pharmacy

Two hundred ninety-nine medication surveillance signals at the start of the NS β-blocker in all participating pharmacies were checked. Patient characteristics are shown in Table 1. The mean patient age was 69.5 years, and 133 (44.5%) were men. A total of 122 (40.8%) patients were examined with asthma, 106 (35.5%) with COPD, and 51 (17.1%) had both symptoms of asthma and COPD. Patients used mostly ocular timolol (39.8%), and the oral preparations propranolol (30.8%) and carvedilol (15.1%).

In 122 cases (40.8%), the pharmacy information system did not generate any medication surveillance signal. In 154 cases, the system generated a contraindication signal (n = 74), an interaction signal (n = 76), or both (n = 4) (Figure 2). For the cases without any signal generated by the system, the lung medication mainly did not appear as actual medication at initiating the NS β-blocker (n = 94) or medication surveillance signals were not used in the pharmacy during the first dispensing (n = 20). For 23 patients, pharmacists could not recall the handling process of the first prescription, mainly due to the lack of digital archiving of handling the surveillance signals in the past. Processing of the medication surveillance signals is shown in Figure 3. In most cases, the patient was informed about the possibility of increased respiratory symptoms (n = 87).

**Figure 2.** Medication surveillance signals, generated by the pharmacy information system.

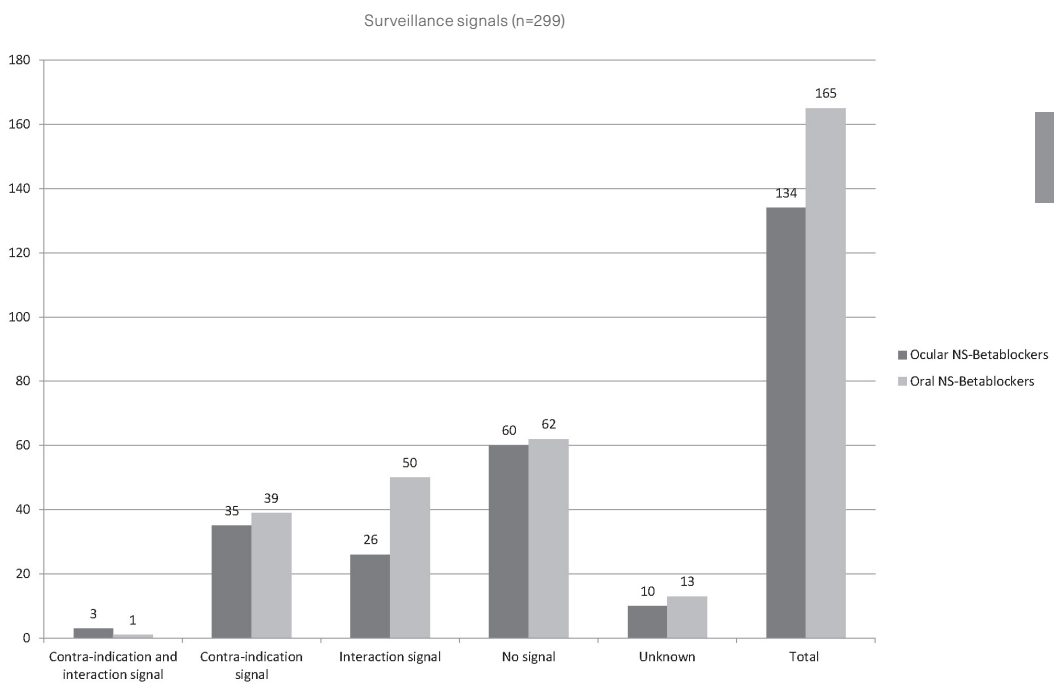
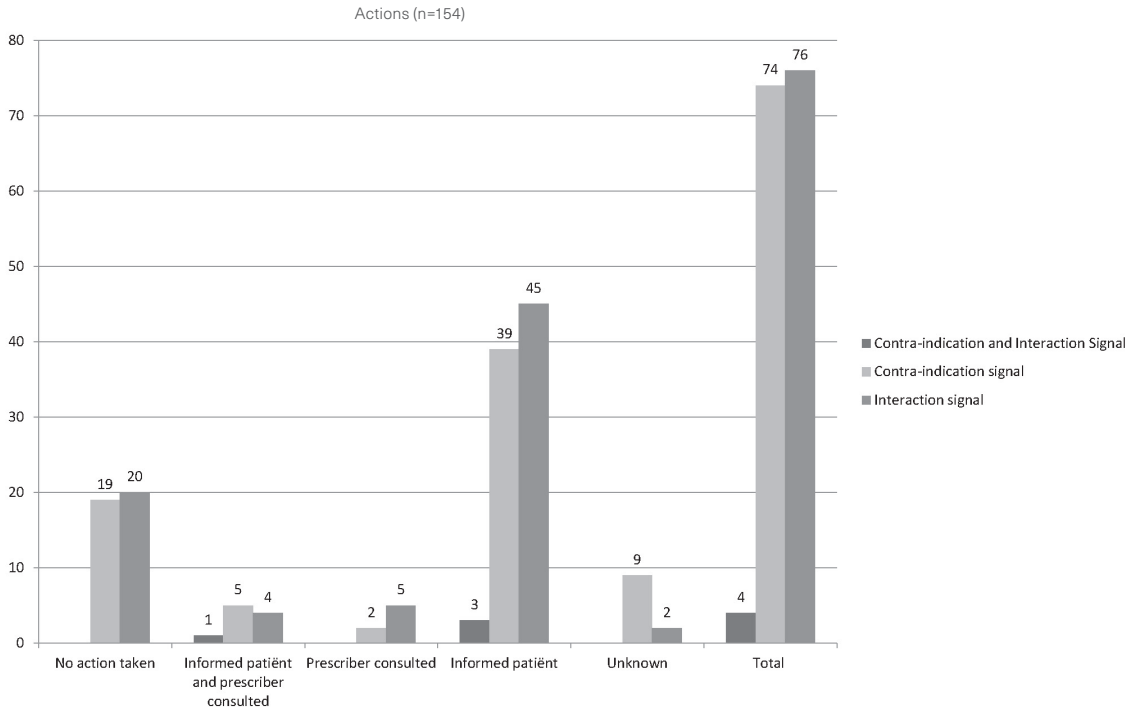


**Figure 3.** Pharmacist interventions on a medication surveillance signal




# Discussion

Our study showed that two-thirds of the interviewed prescribers of oral and ocular NS β-blockers prescribed this medication to asthma or COPD patients deliberately, considering the drug-disease interaction not to be relevant. During the interviews, ophthalmologists argued that they had never seen exacerbations in daily practice, which is not surprisingly as exacerbations are mainly treated by GPs or lung specialist. One-third of the prescribers was simply not aware of the presence of co-morbidity conditions.

Raising awareness and alertness of prescribers for the presences of co-morbidities that might give rise for different choices in drug treatment because of potential contraindications could help to improve the prescribing of NS β-blockers to patients with lung diseases. Additionally, the role of community pharmacists in signalling possible problems due to drugs prescribed by different medical specialists should be emphasized.

Many ophthalmologists held the view that the NS β-blockers can be prescribed despite asthma or COPD. However, despite the relatively low dosage, ophthalmic timolol is more akin to intravenous delivery than to oral dosing, in terms of systemic bioavailability, plasma kinetics, and cardiopulmonary effects (15, 31). Approximately 80% of an ocular administered drop enters the systemic circulation through the highly vascular nasal mucosa, without the

benefit of the first-pass metabolism by the liver (6, 32). Although nasolacrimal occlusion, if applied properly, was shown to be a useful technique to reduce this absorption, it does not completely prevent systemic adverse effects (33-35). A recent meta-analysis showed that ocular dosing with NS β-blockers significantly affected lung function and increased asthma morbidity (14). So there is evidence opposed to the view that the contraindication is irrelevant, and this result is reflected by recommendations from recent studies (14, 15, 36) and the national and international guidelines on the use of NS β-blockers in patients with lung diseases (2, 3). In a recent study, GPs indicated that different factors (e.g. multiple health care professionals involved) contributed to a complex environment, which could result in potentially inappropriate prescribing (37).

The development of clinical guidelines only makes sense, if the care is actually implemented in health care practice. The use of guidelines in daily practice should be evaluated regularly, to identify room for improvement in practice and, if necessary, in the guidelines (38). Our study showed that the implementation of the recommendation to avoid NS β-blockers in patients with lung diseases had led to the general process of medication surveillance signals into the pharmacy information system, but that this computerized signals clearly did not necessarily result in actions by the pharmacists. In 39 of the 154 cases, the pharmacists ignored the signal and decided not to take any action (e.g. consulting the prescriber or adjustment of the therapy). This is consistent with other research on decision support systems in pharmacies (39).



In almost half of the cases studied, pharmacists did not receive any medication surveillance signal in daily practice. Interaction signals were less generated for ocular—than for oral NS β-blockers (26 versus 50 times, respectively). A precondition for an interaction signal is the concomitant use of NS β-blockers and inhalation medication (including β-agonists and ICS). Calculated drug use periods from dispensing information may not correspond with actual patients' drug use. This may be especially the case for both eye drops or inhalation medication, as the daily dose may be accustomed due to symptoms or to the concomitant use of different inhalers or eye drop bottles. In daily practice, this kind of medication history errors is common (40, 41). Combination of pharmacy records and patient counselling could result in an up-to-date and complete medication overview including current medication use and all medication allergies or intolerances, so this can be an important assignment for each community pharmacist.

This study has several limitations. Patient selection and sampling by community pharmacists might have been influenced by individual preferences. Additionally, patients with treatments initiated in hospital might have been missed. Besides, as the prescribers were interviewed about prescribed NS β-blockers in the past, the possibility of recall bias cannot be excluded. For example, this could have led to more socially desirable answers in case of an incomplete dossier, like "the patient has tried alternative medication" or "there was not any lung disease yet." Participating pharmacists were unable to assess whether the prescribers were in the possession of a complete dossier. Furthermore, all selected patients were chronic users of NS β-blockers, which could have led to survival bias; long-

term treatment is more likely to occur in patients who tolerate acute exposure, whereas patients with side effects directly after the start with NS β-blockers are more likely to switch to alternative medication or stop the treatment (14).

Further research is needed to estimate whether NS β-blockers may trigger the development of symptoms, whether this depends on different dose levels of NS β-blockers or the duration of therapy, possible switching of dose levels in the past, or on specific co-medication or co-morbidities. Evaluation of clinical outcomes is part of the implementation process, and this is an important topic for future research.

## Conclusion

In conclusion, this study showed that, in contrast to prevailing guidelines, part of the interviewed prescribers did not assume NS β-blockers to be contraindicated in the selected patients with asthma or COPD. There is no evidence to support this statement, and although the recommendation of avoiding NS β-blockers is implemented in the medication surveillance system in the pharmacy, pharmacists still need to be aware of the evidence-based clinical background of the generated signals and the importance of appropriate handling. Further research is needed to evaluate to which extent the mentioned considerations are legitimate and to estimate clinical outcomes in patients with asthma and COPD, which are (deliberately or unintentionally) treated with NS β-blockers.

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# Appendix I

## Semi-structured format for the interview with prescribers

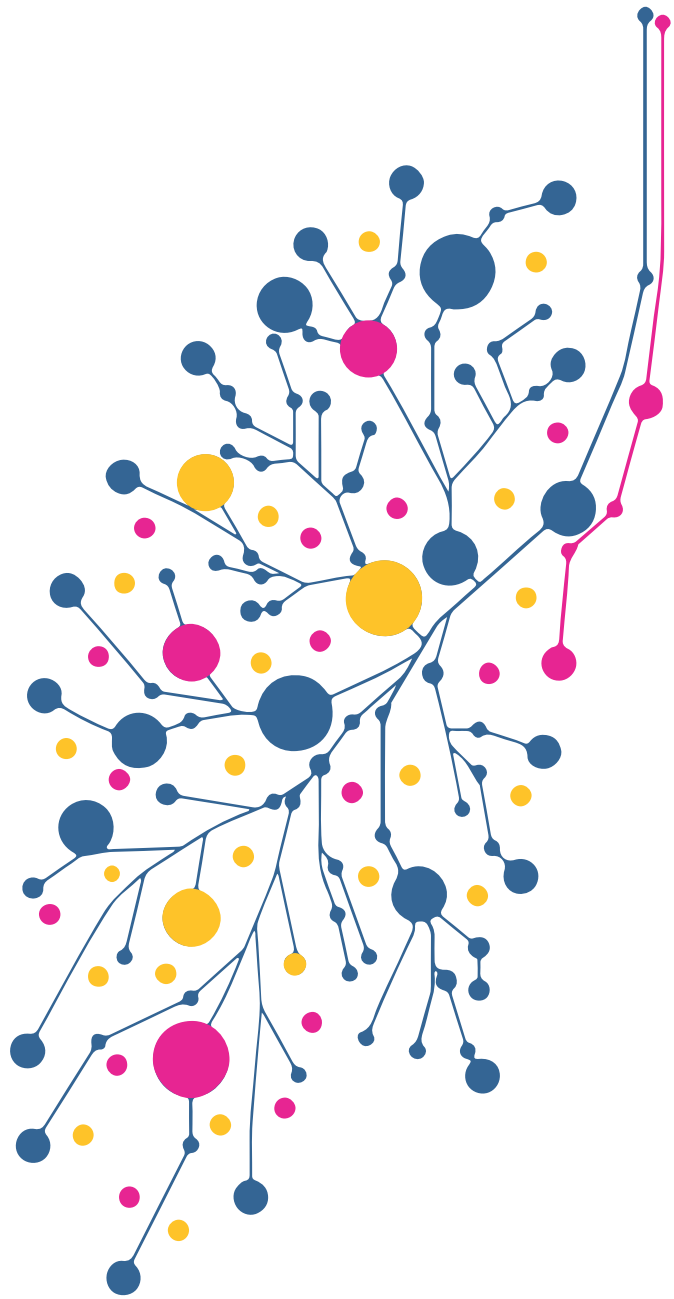
Central question: Was the prescriber aware of the airway disease at the moment of prescribing the β-blocker?

### Yes:

- If so; why did he or she prescribe the non-selective β-blocker despite the contra-indication?
  - Contra-indication not relevant in prescribers' opinion
  - Other medication already tried, but it didn't work
  - There was no alternative
  - Other reason, .....
- If the patient would suffer from exacerbations after the start of the non-selective β-blocker, would the prescriber reconsider his/her choice?
    - If so, what would the choice be for this patient?
    - If not, what are the reasons?

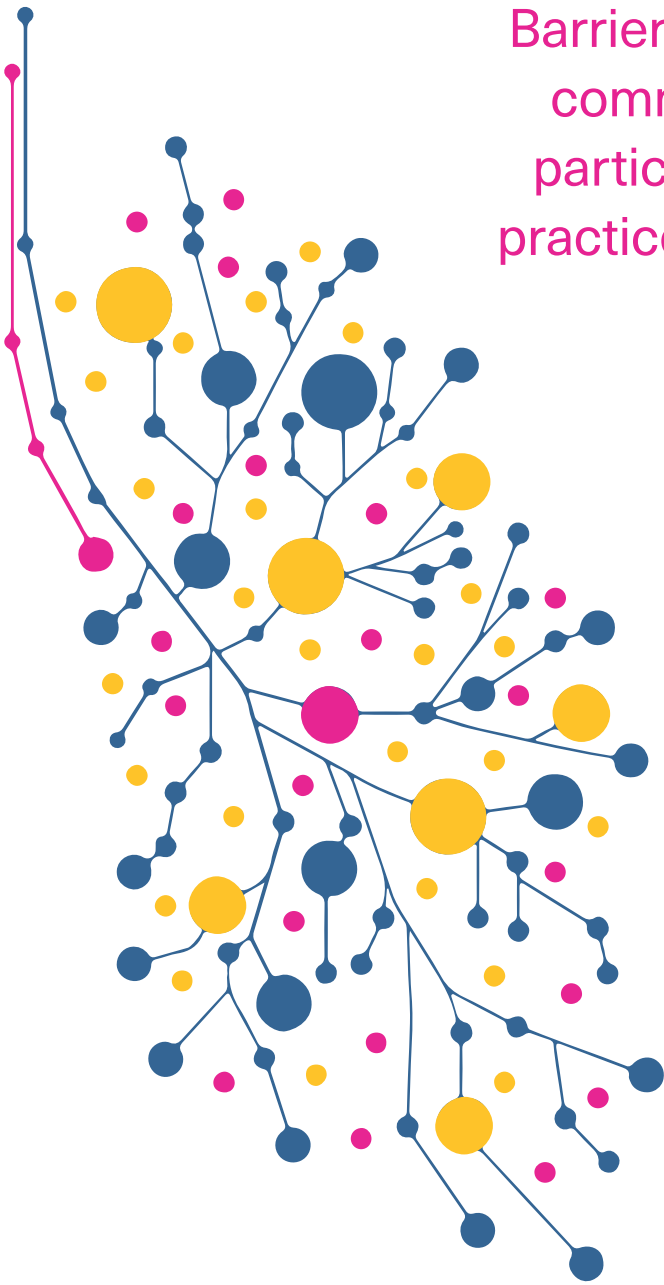
### No:

- If not; what was the possible reason for not knowing the contra-indication in his/her opinion?
- Would the prescriber have chosen an alternative medicine when the contra-indication asthma or COPD was known?
  - If so: which alternative would be chosen?
  - If not: what are his/her reasons?
    - Contra-indication not relevant in prescribers' opinion
    - Other medication already tried, but it didn't work
    - There was no other choice
    - Other reason, .....
- If the patient would suffer from exacerbations after the start of the non-selective β-blocker, would the prescriber reconsider his/her choice?
  - If so: what would the choice be for this patient?
  - If not: what are the reasons?



# Chapter 4

## Barriers and facilitators for community pharmacists' participation in pharmacy practice research: a survey



Esther Kuipers, Michel Wensing, Peter AGM De Smet, Martina Teichert

*Int J Pharm Pract. 2019 Aug;27(4):399-402*

# Abstract

## Objectives

The aim of this study was to explore pharmacists' barriers and facilitators regarding participation in pharmacy practice research.

## Methods

We conducted an online cross-sectional survey in 1974 community pharmacies in the Netherlands.

## Key Findings

A total of 252 pharmacists completed the questionnaire. The majority agreed that participation in research should be part of daily practice. Efficient time investment and a clear benefit for general professional knowledge, patient care and pharmacy organisation were the most important facilitating factors.

## Conclusions

To encourage pharmacists' participation, researchers should offer clear instructions, possibilities for flexible time management, simple patient inclusion, task delegation and no additional contacts with healthcare professionals due to the research.

# Introduction

Effective primary care, based on the relationship between healthcare professional and patient, requires practice research to examine the need, effectiveness and efficiency of specific services that will provide evidence to inform best practices (1, 2). In the past decades, community pharmacy practice has extended the traditional role of dispensing medication to one including provision of patient-centred pharmaceutical care (2, 3). However, conducting practice research and recruiting healthcare professionals to participate in the practice can be challenging. It is essential to accurately grasp pharmacists' views and potential barriers, and prevent dropouts during studies (4). Previous studies have not specifically targeted community pharmacists, and the study results may be outdated (2, 5-7).

The present study aimed to identify community pharmacists' barriers and facilitators in considering participation in pharmacy practice research in the Netherlands. It did so by describing these pharmacists' views and attitudes so as to provide researchers with insight on how to optimize research participation.

# Method



## Setting

Pharmacy students and community pharmacists in the Netherlands are trained to perform research and are regularly invited to participate in pharmacy practice research.

## Survey

A cross-sectional survey was performed in 2017. All pharmacists from 1974 community pharmacies in the Netherlands (8) were invited to complete a 35-item questionnaire. Statements regarding views and attitudes were scored on a 10-point Likert scale. Statements were based on literature (2, 5-7) and researchers' experiences, and all of the present study's authors checked them for face validity. A specific example of a pharmacy practice study was also developed to explore the willingness to participate by varying the (extent of) different potential barriers. The questionnaire ended with an open-ended question on key factors for participation. No personal identifiers were collected.

## Data collection

An e-mail invitation to participate in the survey was sent in July 2017. Non-responders were sent a reminder 1 week later. Data collection was completed at the end of the same month.

## Data analysis

Quantitative data were analysed using descriptive statistics. For each statement, the median and interquartile range were calculated, together with numbers of pharmacists who noted scores of 1 or 2 and 9 or 10. Two of the authors (EK and MT) independently coded and summarised qualitative responses to the open-ended question to identify key topics

via the grounded theory approach (9). Disagreements were discussed until consensus was reached.

## Results

The questionnaire was completed by 252 of the 2968 contacted pharmacists; response rate: 8.8%. Their mean age was 43.7 years, and nearly 48% had recently participated in practice research (within the preceding year).

Table 1 shows the pharmacists' general views and attitudes regarding pharmacy practice research. A majority (85.6%) agreed (score: 7–10 points) that practice research provided evidence-based insight into the activities of community pharmacists, and opportunities for professional development. A majority (71%) also agreed that participation in practice research in general is a natural part of the pharmacists' profession.

**Table 1.** Pharmacists' views and attitudes regarding practice research

| Statement | Median (IQR) | Number of respondents score 1 or 2# | Number of respondent score 9 or 10 | Agree (%)* |
|---|---|---|---|---|
| Participation in pharmacy practice research belongs to the profession of every community pharmacist | 8 (2) | 13 | 57 | 179 (71.0%) |
| Participation in pharmacy practice research belongs to the education of a community pharmacy specialist. | 8 (2) | 10 | 88 | 220 (87.3%) |
| Without pharmacy practice research the specialism of the community pharmacist cannot exist for the long term. | 7 (2) | 17 | 54 | 162 (64.3%) |
| Pharmacy practice research provides evidence-based insights in the actions of the community pharmacist. | 8 (2) | 7 | 83 | 216 (85.7%) |
| Pharmacy practice research provides insights in future opportunities for the profession of the community pharmacist | 8 (2) | 4 | 75 | 209 (82.9%) |
| I would like to participate in pharmacy practice research, but it is too busy in the pharmacy. | 7 (3) | 28 | 47 | 139 (55.2%) |
| I only participate in pharmacy practice research if the subject is interesting enough for me. | 8 (1) | 8 | 55 | 198 (78.6%) |

**Table 1.** Continued

| Statement | Median (IQR) | Number of respondents score 1 or 2# | Number of respondent score 9 or 10 | Agree (%)* |
|---|---|---|---|---|
| If the subject is also important for the general practitioners (GP's) I am working with, I only participate if patients' GP has no objections. | 7 (4) | 31 | 36 | 127 (50.4%) |
| I am willing to find time to participate in pharmacy practice research. | 7 (3) | 20 | 25 | 130 (51.6%) |
| I only participate in pharmacy practice research if have confidence in the investigators. | 8 (2) | 5 | 73 | 190 (75.4%) |
| I only participate in pharmacy practice research if it is obliged (e.g. during education). | 4 (4) | 80 | 6 | 38 (15.1%) |
| If I participate in pharmacy practice research depends on my employer. | 5 (5.75) | 73 | 25 | 84 (33.3%) |
| I only participate in pharmacy practice research if I know the investigators personally. | 3 (3) | 124 | 0 | 6 (2.4%) |
| I am convinced of the added value of pharmacy practice research. | 8 (2) | 4 | 65 | 192 (76.2%) |
| **Participating in pharmacy practice research...** | | | | |
| Is generally interesting for me. | 7 (2) | 13 | 49 | 188 (74.6%) |
| Gives me opportunities for personal development as a pharmacist. | 8 (2) | 11 | 46 | 183 (72.6%) |
| Is feasible in the pharmacy where I am working. | 7 (3) | 22 | 28 | 128 (50.8%) |
| Is usual procedure in the pharmacy where I am working. | 5 (3) | 63 | 17 | 73 (29%) |
| Is stimulated by colleagues or the professional group. | 6 (3) | 29 | 12 | 83 (32.9%) |
| Can help me to improve patient care and my relation with patients. | 7 (2) | 6 | 29 | 167 (66.3%) |
| Can help me to improve my position as healthcare professional. | 8 (2) | 4 | 65 | 202 (80.2%) |

# total number of respondents per statement: 252
*Scores 7-10
IQR: Interquartile range

Almost 51% of the respondents felt participation was feasible in daily practice, and 29% regarded participation as common for their daily practice. Additionally, 55% indicated

they would like to participate but lacked the time to do so. Important facilitators were confidence in the investigators and interest in the study topic (75.4% and 78.6% agreement, respectively). Although a majority (76%) of the respondents reported being convinced of the general added value of pharmacy practice research, only 52% indicated they were prepared to invest the time to participate.

The surveyed pharmacists expressed they were more likely to participate in practice research when the requested work could be spread over some weeks rather than performed in 1 day (77.4% vs. 35.3%, respectively; Table 2). They also preferred the possibility of delegating tasks (e.g. to their pharmacy technicians) over performing all procedures themselves (90.9% vs. 61.9%, respectively). They were more likely to participate when patients could be invited by email (86.8%) instead of personally during pharmacy visits or by telephone (65.9%). Pharmacists can access patients' email addresses, as most pharmacies offer digital services (e.g. track and trace). The need to cooperate with medical specialists discouraged more than half of the surveyed pharmacists; only 48% would participate, compared with 73.8% when cooperation only with general practitioners was required.

**Table 2.** Case: organisational factors and influence on participation (n=252)

*You are invited to participate in a pharmacy practice study about the implementation of specific clinical rules. You have to include 5 patients, obtain their informed consent and collect data as well by a short questionnaire as from the pharmacy information system. The anonymous data have to be registered in a predefined form and should be sent digitally to the investigators. The estimated total time investment is about 5 hours.*

| **Would you participate in the described study if:** | **Yes (%)** |
|---|---|
| The total investment of time has to be done on one day? | 89 (35.3) |
| The total investment of time has to be spread over a period of three weeks? | 195 (77.4) |
| The study has to be finished within four weeks from now? | 169 (67.1) |
| The study has to be finished within twelve weeks from now? | 200 (79.4) |
| All tasks have to be done by the pharmacist? | 156 (61.9) |
| You can delegate a part of the tasks? | 229 (90.9) |
| There is no financial compensation? | 159 (63.1) |
| During the study cooperation with the general practitioner is required? | 186 (73.8) |
| During the study cooperation with a medical specialist is required? | 121 (48.0) |
| You can invite all patients for participation directly in the pharmacy (no selection needed)? | 211 (83.7) |
| You have to make a selection before inviting patients yourself? | 203 (80.6) |
| You can invite patients for participation by email? | 219 (86.9) |
| You can invite patients for participation only personally or by telephone? | 166 (65.9) |

A total of 415 key factors for participation were mentioned. The cluster of factors identified most frequently were total time investment, timing of the study and the possibility of flexible time needed to participate (n=142). These were followed by need for clear added value (for the profession, the patient and the pharmacy practice or pharmacist, n=104). Specifically mentioned positive factors (n=67) were simple patient selection and data collection, no need for cooperation with many different healthcare professionals, a clear and complete description of the required tasks, no collection of superfluous data, and reliable explanation of the study and the activities required.

## Discussion

The present study results offer clear guidance for designing pharmacy practice studies. Researchers should pay close attention to efficient time investment and study logistics, for example possibilities of inviting patients by email, delegating tasks and spreading out time investment. This study corroborates results of earlier studies (2, 10). When pharmacists were convinced of a study's added value and feasibility, they reported willingness to invest their time, even when no financial compensation was available. However, obligated contact and cooperation with other healthcare professionals was a discouraging factor in participating in practice research.



A limitation in the present survey was the low response rate, which reflected the problem addressed herein. As expected, respondents had recently participated in pharmacy practice research. The results cannot be generalised to all community pharmacists because of this selection bias. However, the opinions of experienced and interested respondents were of great importance. Committed pharmacists experienced limited support from colleagues or professional organisations; thus, there are still possibilities to actively boost participation.

## Conclusion

Pharmacists' participation in practice research depends on the research design. Clear descriptions, possibilities for flexible time management, simple patient inclusion and task delegation can all increase this participation. Researchers should acknowledge that cooperation with many different healthcare professionals may pose a barrier towards participation in practice research and should develop strategies to address this.

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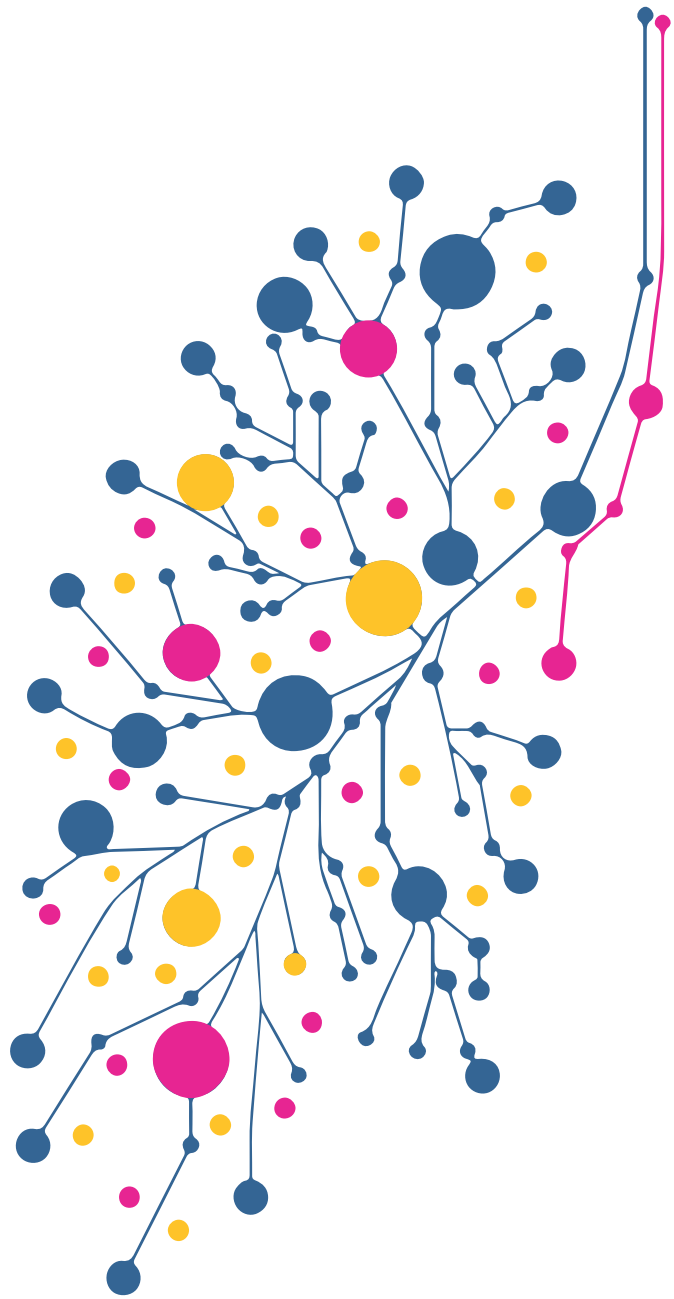
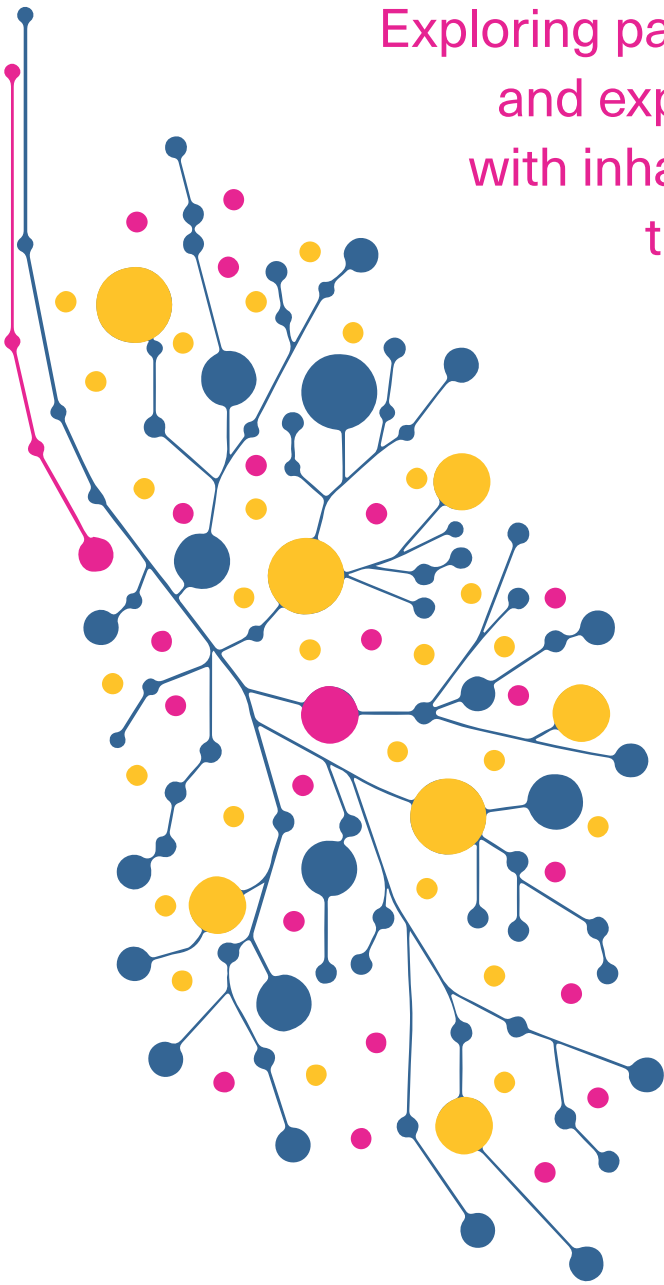


# Chapter 5

## Exploring patient's perspectives and experiences after start with inhalation maintenance therapy: a qualitative theory-based study



Esther Kuipers, Michel Wensing, Peter AGM de Smet, Martina Teichert

*Submitted*

# Abstract

## Background

Treatment of obstructive lung disease with inhalation therapy needs changes in patient behavior. Shortly after the start with inhaled corticosteroids (ICS) maintenance therapy, patients might be in need of additional pharmaceutical care, tailored to their individual needs.

## Objectives

This study aimed to provide insight into patient behavior, goals and perceptions regarding their medical treatment at start with ICS therapy, by telephone interviews with ICS starters. Besides, this study investigated pharmacists' and patients' experiences with these interviews and opinions on the utility of this type of consultation for daily practice.

## Methods

Semi-structured telephone interviews were conducted by pharmacists with adult patients 2-3 weeks after starting ICS. The Theoretical Domain Framework (TDF) was used for data analysis and coding. Afterwards, the patients and pharmacists were questioned about their experiences with the interview.

## Results

Five pharmacists conducted interviews with 23 ICS starters. Except the domains 'environmental context and resources', 'optimism', and 'reinforcement', the remaining 11 domains in the TDF were addressed in the interviews. The majority of patients defined personal goals, which mainly addressed disease or symptom control (clinical goals). Some patients showed a lack of knowledge regarding the clinical indication or therapy duration. Views on beneficial medication effects differed between patients. Some patients specifically mentioned concerns or anxiety about side effects. The interviewees described different perceptions on the necessity of a personalized routine for regular medication use. Patients and pharmacists both felt positive about an added value of these interviews for daily practice.

## Conclusion

Patient interviews shortly after start with ICS therapy revealed various perceptions and beliefs that might influence medication use and achievement of individual treatment goals. The patients appreciated the opportunity to ask questions and share their perspectives and needs with their pharmacist, and the pharmacists experienced that the interviews had added value.

## Introduction

Daily use of inhaled corticosteroids (ICS) is effective for patients with obstructive lung diseases in the reduction of symptoms and the frequency of exacerbations (1, 2). The behavior of taking medication for a chronic disease is a complex and dynamic process (3), and inhaled therapy has additional challenges for patients in daily practice (4). Both the inhaler device technique and patient adherence to ICS are crucial in the effectiveness of the medical treatment (5-8). However, patient adherence to ICS is shown to be generally poor (9-12), and many patients experience problems in achieving and maintaining the correct inhaler device technique (5, 6, 13-15).

Patient support programs, such as medication management and counseling, have the potential to improve patient's disease control and medication adherence (16, 17). A previous pharmacist intervention study has shown a positive impact on patients' knowledge about asthma and medication (18). Other studies have shown that pharmacist interventions were effective in improving the inhaler device technique skills (19, 20), and a randomized controlled trial demonstrated that pharmacist interventions improved both medication adherence and inhaler device technique in patients with chronic obstructive pulmonary disease (COPD) (14). However, pharmacists' interventions in these studies mainly focused on improving patients' knowledge or practical skills by providing protocol-defined information or education, rather than being tailored on patients' individual needs or goals.



As patients differ fundamentally in coping with their chronic disease, there might be more individual barriers that hamper optimal medication use, which need different techniques to change behavior. For example, beside knowledge of their disease, asthma patients reported different beliefs about the consequences of their condition and the necessity of the medication prescribed (21). Additionally, fear and worries about short- and long-term side effects of treatment, including safety of the medication and addiction to it, were related to poorer adherence (22). In patients with COPD, the knowledge of ICS and potential side effects was shown to be limited (23). Besides, patients' beliefs and expectations about therapy, and the complexity of the dose regimen (eg frequency of administration) influenced medication use (24, 25). The Theoretical Domains Framework (TDF) has been developed to summarize possible determinants to address factors that influence behaviour, from a behaviour change psychology perspective (26, 27). This framework can be used as a theoretical basis to identify and develop theory-informed behaviour change interventions (26, 28, 29).

Taking medication is a complex behavioral process, and a previous study has shown that non-adherence to medicines for chronic conditions may develop shortly after the start of medication (30). So this period is an important time window for pharmacist interventions; patients may be in need of counseling and support, while being highly focused on their health and new therapy (31). Earlier studies have shown that questioning patients during the first refill of a medicine could encourage patients to report how they experienced their medication use and if they had drug-related problems (32, 33). At present, the pharmacy

staff mainly plays a role in organizing the logistics of repeat prescriptions (34, 35), but exploring patients' experiences with the medication is not yet routine in daily practice (36). However, especially with inhaled medication, the recognition of (adherence) problems could be delayed, as refills with inhalers containing a large number of doses (eg 200 doses in some pMDIs) could take some time. Consequently, consultations shortly after the start of inhaled maintenance medication may be useful to explore patients' personal goals, discuss medication experiences, concerns, questions and problems. However, such care is not yet part of daily practice, and little is known about the utility and feasibility of these consultations, and the best way to conduct them.

This study aimed to provide insight into personal goals, patient perceptions and beliefs regarding the medical treatment for their obstructive lung disease in patients who just started their drug therapy, by a telephone interview with their pharmacist. Furthermore, this study aimed to evaluate the experiences of patients and pharmacists on the utility of these interviews.

# Methods

## Design

This was a qualitative study based on telephone interviews performed by five pharmacists from five community pharmacies in the Netherlands between July and December 2018. Reporting of the study follows the relevant sections of the consolidated criteria for reporting qualitative research (COREQ) (37).

## Setting

The participating pharmacists were recruited by convenience sampling in the researchers' network. They had a special interest in pharmacy practice research and lung diseases (eg, as member of the special interest group 'lung diseases' of the Royal Dutch Association for the advancement of Pharmacy (KNMP)). In the Netherlands pharmacists have a professional and legal responsibility to enhance the safety and efficacy of their patients' drug treatment. As most patients in the Netherlands adhere to one community pharmacy, pharmacists usually dispose of complete prescription histories of their patients (38, 39).

In community pharmacies in the Netherlands, patient counseling is usually linked to the moment of the first dispensing and first refill (ie second dispensing) of the medication. The pharmacy staff generally consists of pharmacists (educated in 6-year university programs) and pharmacy assistants, who were educated in 3-year vocational programs (40). In contrast to the first dispensing consultations, which mainly aim to provide practical information and technical instruction to the patient, during the second and subsequent dispensing encounters, the pharmacy staff ideally ask for patients' experiences with the medication (41).

## Ethical approval

The study protocol was approved by the Ethical Committee of the Radboudumc Nijmegen (approval number, 2018-4381). All the procedures were in accordance with the requirements for studies involving human participants, with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Prior written informed consent was obtained from all individual participants included in this study.

## Patient inclusion

Patients were screened and selected during the first dispensing by the prescription checks of the pharmacists or by a search strategy in the pharmacy information system. The pharmacists invited all patients >18 years of age who received a first dispensing of ICS or the combination of an ICS and a long acting beta agonist (LABA); Anatomic Therapeutic Chemical (ATC)-codes: R03BA, R03AK06, R03AK07 and R03AK08 (42). A first dispensing was defined as a dispensing of a new prescription in the absence of a dispensing for ICS during the previous 12 months. Patients were included if they spoke, read, and wrote Dutch sufficiently well.

Patients fulfilling the inclusion criteria were informed of the study personally at the moment of the first dispensing encounter or by telephone within one to two weeks afterwards. The patients also received written information and an informed consent form. If the patient was willing to participate and provided informed consent, the pharmacist made an appointment for a telephone interview. Anonymized data about gender, age, type and dose of medication were obtained from the pharmacy information system.



## Patient interview

The interviews were performed by the five community pharmacists (including one of the researchers (EK)) in their pharmacy. The telephone interview was semi structured, allowing interviewees to respond in their own words. The content of the telephone interview guide (Appendix A) was based on the existing literature and recommendations from national pharmaceutical guidelines regarding the dispensing encounters (41, 43, 44). The information collected was about symptoms and disease control, the experiences with medication use in daily practice, patients' personal goals, and disease and treatment related concerns and personal questions (eg side effects, concerns). Each interview took about 10-15 minutes.

## Estimation of the utility of the interviews

At the end of the interview, patients were asked how they felt about the interview. Besides, all pharmacists were questioned about their experiences with the patient interviews, regarding the feasibility in daily practice (time investment, organizational factors), and their ideas about the utility and opportunities for providing additional care (for the topic list: see Appendix A). All interviews were conducted in Dutch.

### Data analysis

All interviews were digitally recorded and transcribed verbatim. Data analysis was facilitated by Microsoft Office Excel. Data were analysed using an iteration of inductive and deductive steps in a thematic approach (45). In the first phase of the analysis process, two members of the research team (EK and MT) started with an inductive approach by several readings of the transcripts to become familiar with the data and check the appropriateness of the 14 domains Theoretical Domains Framework (TDF) (27) for analysis. During the deductive second phase, themes regarding the perceptions and beliefs regarding medication used were defined and organized into the TDF domains. Each theme was reviewed for content and allocated into relevant domains of the TDF, or recorded as not fitting into any of the TDF domains. One member of the research team (EK) read and coded the transcripts. A second member (MT) independently coded a sample of the transcripts (approximately 40%). Discrepancies were discussed until consensus was reached. Illustrative citations were selected for each of the domains. After 23 interviews no new themes were derived from analysis and data saturation was achieved (46, 47). In the final phase, it was checked whether there were text fragments that could not be categorized within the TDF, but this was not the case.

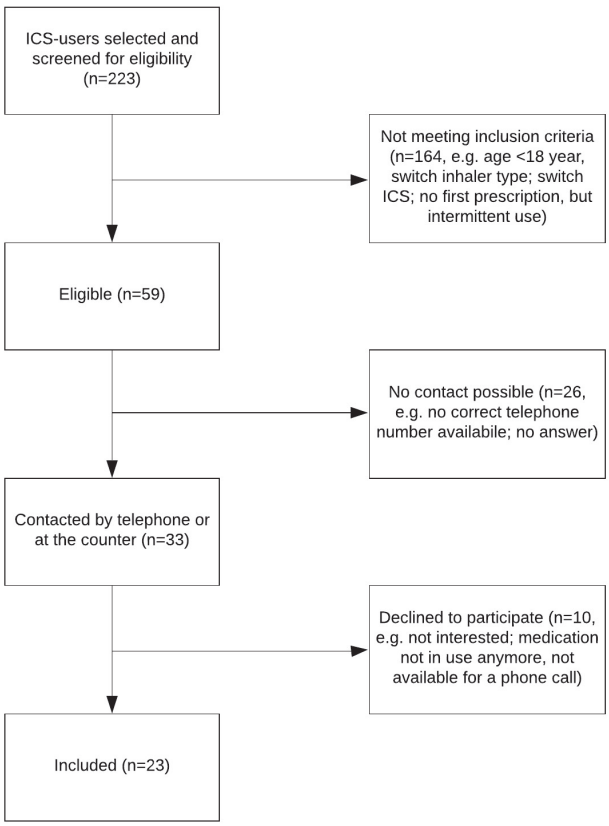
## Results

### Participants

In five pharmacies, 223 ICS-users were initially selected and screened for eligibility (figure 1). 164 patients did not meet the inclusion criteria, for example concerning their age, or because they switched from an ICS to a combination of ICS/LABA. 59 patients were eligible. From those pharmacists contacted a first group of 33 patients, of whom 10 did not participate. This was due to refusal from the beginning or due to later drop out. For example: one patient initially agreed to participate, but did not answer the phone at the moment of the appointment and was not available anymore. In total 23 patients were interviewed for the study (table 1) within 2-3 weeks after starting the ICS. The mean duration of the interviews was about 11 minutes (range 4 to 29 minutes).

All five interviewers were female and they were practicing pharmacists, with working experience in the community pharmacy between 1 to 15 years.

**Figure 1.** Flowchart patient inclusion




ICS: inhaled corticosteroids

**Table 1.** Patient characteristics (n=23)

| Characteristic | Value |
|---|---|
| Age (years), mean (range) | 56.3 (20-84) |
| Female, n (%) | 19 (82.6) |
| Inhalation maintenance medication, n (%) | |
| Beclomethasone/formoterol | 6 (26.1) |
| Budesonide | 1 (4.3) |
| Budesonide/formoterol | 1 (4.3) |
| Ciclesonide | 8 (34.8) |
| Fluticasone | 5 (21.7) |
| Salmeterol/fluticasone | 1 (4.3) |
| Vilanterol/fluticasonfuroate | 1 (4.3) |
| Type of inhaler, n (%) | |
| pMDI | 19 (82.6) |
| DPI | 4 (17.4) |

## TDF Domains

Of the 14 TDF domains, 11 domains with possible influence on patients' medication use behavior were covered, except the domains 'reinforcement', 'optimism', and 'environmental context and resources'. The domains with illustrative quotes are presented in table 2.

Some patients reported a lack of knowledge of the clinical indication, the duration of therapy, or doubts on the right indication. The extent of knowledge on potential medication side effects and prevention differed strongly between the patients. Some patients reported that they were well-informed, while one patient specifically mentioned that she did not know anything regarding the possible side effects, but that she would possibly be more interested in the side effects when experiencing unexpected effects. Patients had different perceptions on the effect of medication; some patients doubted an effect, while others were convinced of a beneficial effect. The perceived necessity of the medication was higher when patients experienced a reduction in symptoms. Some patients reported that using their pMDI with a spacer was easy and that they never experienced any problems, while others described some difficulties with the inhaler technique. Patients' beliefs about capabilities included their beliefs about their physical or technical capability and skills to use their inhaler, but also beliefs about the capability to organize using the inhaler in daily life.

The majority of respondents mentioned that they already had developed a personalized routine for using the medication, for example by linking the inhalation to meal times, the moment of tooth brushing, or bed time. Almost one third of the patients used practical reminder strategies: they placed the medication in a visually prominent place (eg on the

kitchen table or near the sink). One patient used an eHealth application on her mobile phone, which contained a reminder function.

Patient autonomy was considered an important identity factor; respondents regarded medication use as their own responsibility. This was expressed in different situations; for example one patient had never used the inhaler with the spacer, because she did not want to. Another patient tried to use the inhaler without a spacer, but experienced that the medication was less effective and decided that the spacer was really necessary for her. One patient mentioned that she used her medication according to the frequency prescribed, but she wanted to choose her own time during the day to use the medication. A few patients decided or doubted about reducing their daily dose or stop the medication without consulting any healthcare professional, when they felt that there was no need to continue.

Although some patients reported that they never forgot to take their medications as prescribed, there were also people admitting that this happened sometimes. It seemed more difficult to pay attention to medication specifically when patients were out of normal context, for example during weekends or on holidays.

The majority of patients (20 of the 23) described personal goals. 2 patients described goals to reduce the total number of prescribed medications. However, most patients mentioned that their condition had impacted their lives and they aimed clinical goals, like the improvement of symptoms and disease control.



During one of the conversations, there were several signals that the patient (male, 84 years old) experienced difficulties in organizing his life in general. During the conversation, the patient seemed to be a little bit confused and he could not answer all questions clearly *("I don't know where my inhaler is"*, or *"I think I have to use it twice a day, but to be honest: I don't know."*). There were signs on impairment in both mental and physical skills to use all medication as prescribed and the patient received help from his wife. However during an additional interview with his wife she reported that she found it difficult to support her husband with the use of the inhalation medication: "*The inhaler that he received from the doctor, he actually didn't use it at all. It is completely new. I don't know why. The inhaler is actually the only medicine that I'm not involved with very much."*

**Table 2.** TDF domains and illustrative quotes

| Domain | Themes | Illustrative quotes |
|---|---|---|
| **Knowledge** | Knowledge of the clinical indication, the duration of therapy, or doubts on the right indication<br>Knowledge of potential medication side effects (and prevention) | *"And then I thought: 'well, do you have to persist for six weeks? Or can you stop if you do not feel it anymore?' I actually did not know that." [P20]*<br>*"I did not read the leaflet; because I only read a leaflet when I experience things of which I think: 'hey, I do not have that normally'." [P14]*<br>*"No, I do not rinse [my mouth after inhalation], but I always take it [the medication] before breakfast. So actually I think that [taking it] with the breakfast, this maybe might have the same result [in preventing side effects]?" [P7]* |
| **Skills** | Inhaler technique<br>Organizing life in general | *"Well, sometimes I notice that I am inhaling too hard. So then he [the spacer] will beep. And then I think: 'oh yes, wait a bit, a little bit slower'. And then it goes well." [P16]* |
| **Social/professional role and identity** | Patient autonomy ('medication use is my own responsibility') | *"I do not use that [spacer]. Well, I did not like this. No, I did not even try it at all." [P6]*<br>*"No, then I have to watch the clock, I do not like that."[P1]*<br>*"Yes, the last couple of days I only did it [taking medication] before the night, because I experienced that I had a cough in the evening, but not in the morning. Yes, I still benefit sufficiently from that." [P11]*<br>*"I do have not really a question, but just.. I had to use it for a month. But I feel that.. If it helped me, I actually want to stop and see what happens. And if it [symptoms] comes back, then yes, I will take it again." [P14]*<br>*"So I did not use it for 4 or 5 days and then I felt that it [shortness of breath] was coming back. So then I just started puffing again and now I use it every day again." [P20]* |
| **Beliefs about capabilities** | Physical or technical capability<br>Organizing inhaler use in daily life | *"I think that inhaling does not have to be that hard. But of course it is important that you receive proper instructions." [P23]* |
| **Beliefs about consequences** | Concerns about consequences of long term ICS use or possible side effects.<br>Perception on the effects of medication<br>Perceived necessity of medication | *"Of course I have read over side effects in the leaflet, so I was a bit worried about that. I hoped that I would not … that it [sleeping problems/anxiety complaints] would not bother me again. [P23]*<br>*"If I do not see any results, when I just stay that tired and the coughing continues. Then I think: 'well, how much sense does it make?" [P10]*<br>*"Because I was always wheezy and now, I can just breathe again. I actually like it." [P15]*<br>*"I need it [the spacer], because I must say that otherwise it [the medication] does not help that much." [P4]* |

**Table 2.** Continued

| Domain | Themes | Illustrative quotes |
|---|---|---|
| **Intentions** | Intention to use medication, intrinsic motivation | *"I think I have to use it properly, because otherwise it makes no sense." [P13]*<br>*"Well, probably because I have never had any medicine, I feel like: 'yes, I have to do this properly'." [P1]* |
| **Goals** | Reducing number of prescribed medications<br>Clinical goals | *"[My goal is] that I have enough breath. That I can do everything intensively, like I always did: my work-out, riding a bike, playing at home with the children, climbing a staircase. Just that I have enough breath."[P20]* |
| **Memory, attention and decision processes** | Forgetting medications<br>Paying attention to medication out of normal context | *"Well, I forget it sometimes" [P12]*<br>*"Eh yes, during the weekend I am having a lot of fun. When you went to bed late the night before, then in the morning you are not always that fresh, and sometimes I do not succeed [in taking medicines]." [P7]*<br>*"Well, [I was] a little bit nervous, we were in a small house with children and so on. So I thought: 'I have to sit down quietly and [learn] on my own way how to deal with it." [P10]* |
| **Social influences** | Social support or pressure from family<br>Involvement or pressure from healthcare professionals | *"I only take it; my wife put it ready for me." [P2]*<br>*"Of course I cannot return to the pulmonologist and say: 'well, I tried it for 8 days, but then I was not in the mood anymore'." [P10]* |
| **Emotions** | Anxiety about the possibility of having an underlying disease | *"To be honest, I must say that I get scared. Because you read and hear it regularly: people are tired, are coughing for a long time, and yes, then suddenly it turns out to be lung cancer. I experienced that one and a half year ago with my mother. She coughed too, and at one moment there was also blood. And then she had lung cancer. And yes, that stays in my mind." [P19]* |
| **Behavioral regulation** | Personalized routine<br>Practical reminder strategies<br>eHealth applications | *"I also brush my teeth every night, so I just do it before the tooth brushing."[P22]*<br>*"I have to do is twice a day, so then it is one time in the morning and one time in the evening, not at fixed times." [P14]*<br>*"Well, look, I have downloaded an app, I believe it is called 'my therapy', where you can set that you have to take your medication. I programmed that and I get a very nice whistle at the times that I have to take it. And I also get.. It also gives you.. Let's say, if you are opening your telephone, then you can see that you still have to take it [the medication]." [P23]* |

### Experiences with the interviews

Eighteen patients were asked for their opinion regarding the interview with the pharmacist. All of them felt positive and some patients specifically mentioned that they have liked sharing their experiences with the pharmacist or asking their questions: *"It was a good conversation, nice and smooth. And I always feel when talking with a doctor: 'you may not lie about medication use'. But yes, I am busy and then I do not succeed [in taking medicines] and then I feel embarrassed [to tell]. But I didn't get that idea now, and I really like that." [P7]*

*"Well, I am glad that I was able to tell briefly my concerns."[P19]*

Patients regarded an additional telephone consult with the pharmacist to be useful, even when they personally did not have problems or questions at that moment: "*It is good to ask those questions, because there are people who have troubles. Not me, but it is good that those questions are being asked." [P5]*

All pharmacists felt positive about the interviews. Conducting the interviews was reported to be feasible in daily practice; the time investment of the patient interviews was manageable and acceptable for all pharmacists. Two of the pharmacists reported to have experienced difficulties with the selection of patients and they initially found a lot of patients who were not eligible. All pharmacists felt that these telephone consultations, shortly after the start of ICS, could potentially have an added value to the patient (eg the opportunity to share their experiences and ask questions shortly after the start), but also to themselves (eg the opportunity to obtain early insights in patients' thoughts and motivation regarding their medication use). *"One patient said to me: 'I actually do not notice any effect.. I don't know if I should continue, what should I do?' At the moment it felt good to provide appropriate information." [A4]*

## Discussion

This study provided insights in the perceptions and beliefs regarding medication use of patients shortly after their start with ICS maintenance therapy in obstructive lung diseases. Telephone interviews in this study revealed various perceptions that might influence the achievement of individual treatment goals and showed opportunities for additional pharmaceutical care after starting with ICS.

Patients shared much personal information during the interviews. They revealed various factors influencing the perspectives regarding their medication and condition, which might have hampered optimal medication use (now or later). 11 of the 14 TDF domains were covered by the information from 23 interviews. Patients reported different perceptions and beliefs on the effect of medication and although some reported that they had always taken their medications as prescribed, others admitted that they did not (either intentional or unintentional). Some patients reported that they already had developed a routine for using the medication daily, while others were still searching for such a routine. In earlier studies,

building a habit was stated to be useful for overcoming forgetfulness, and also lengthen medication persistence (ie the length of time between initiation and discontinuation).[48]

Separating pharmaceutical care from the medication delivery process might provide more timely insights in patients' needs and wants. Some important information that patients reported during the interviews would not have been emerged during standard counseling at the pharmacy's counter. Pharmacists' interventions in earlier studies focused on the domains of knowledge and skills (14, 18-20). Our study showed additional individual barriers or facilitators, that might influence the behavior of medication use. Personal goals, concerns about side effects or emotional factors would probably not have been asked and discussed during the regular encounters. Earlier studies have shown that the pharmacy staff is generally used to provide practical information and technical instruction, but do not often discuss patient's preferences and perceptions about prescribed medications (49, 50), or stimulate patients to ask questions (50-55).

All responding patients in this study felt positive about the interview and although not all patients reported to be in need of additional care, they appreciated the moment of personal attention and often reported that this evaluation moment was of added value for them. Also all pharmacists experienced the interviews generally as beneficial for the patients and for themselves. Although this type of counseling is not routine, all of them were positive about the interview and they regarded this type of consultation as feasible in daily practice. They felt that additional telephone pharmacist consultations in daily practice gave them opportunities to grow in applying a patient-tailored approach, and to focus on exploring patients' individual needs and wants, rather than only providing practical information. Both patients and pharmacists reported that they saw an added value of the pharmacists' consultations and that these could possibly provide information for future tailored interventions related to personal goals, side effects and behavior for medication use.



## Strengths and limitations

This study emphasized the added value of an early evaluation of patient's beliefs and perceptions, shortly after the start with ICS; patients mentioned several issues that were judged to need additional pharmaceutical or medical care. Although it is practically impossible to check patients' inhaler technique during a telephone interview, patients were invited for a check in the pharmacy if there was a signal that they were in need of that. Judging from these consultations, the pharmacists could not have estimated in advance which patients were in need of additional pharmaceutical or medical care. It could not be deduced from a person's pharmacy record whether additional care was needed. So, pharmacists can gather relevant information from and about their patients if they practice this kind of consultation.

There are some limitations to this study. First, in this convenience sample the majority of the participants was female, which might hamper extrapolation of the findings to other individuals. Based on the general data of ICS users in the pharmacy population, we had

expected that a lower percentage (55-60%) of the participants would be female. During the inclusion the women appeared to be more willing to participate. Although there was a broad age range (20-84 years), younger people were also underrepresented in the sample. There were less starters with ICS in the age group 18-50 than in the group aged >50 years. This may be explained by the fact that it is likely that younger patients had been diagnosed with asthma during childhood. However, although the proportion of male – and younger participants was lower than expected, the research team remains confident that the patients illustrated a broad range of experiences and that interviewing was continued until data saturation had been met. This is also reflected in the broad range of identified TDF domains. Besides, this study only included patients who started with ICS: the patients that had switched their medication or inhaler device were excluded. However, this latter population could also comprise patients in need of additional care, as switching could indicate suboptimal therapy. Second, although the TDF covered most of the data, some of the identified themes were strongly related, and therefore could be coded to more than one domain, depending on the patients' context. For example: the wife's role in the situation of the earlier described case (ie the confused man, possibly demented), is related to the domain of social support, but also interfaces with the domains of skills (mental and physical skills to organize life in general) and memory, attention and decision processes. Third, it appeared to be difficult for the pharmacists to enter the selection criteria completely in the searching module of the pharmacy information system. It was not possible to select the age and the system did not recognize immediately whether patients had switched between different inhaler types or ICS and ICS/LABA combinations. Consequently, the selection had to be checked manually and the majority of people from the initial selection seemed not eligible. This was also mentioned by the pharmacists; the selection of patients took more time than expected.

## Conclusion

Telephone interviews conducted by community pharmacists shortly after start with ICS maintenance therapy revealed various behavioral barriers that might influence the achievement of individual treatment goals. Patients shared important information, which probably would not or incompletely have emerged during encounters in regular daily practice. Both patients and pharmacists were positive about the interviews. Pharmacists felt that telephone consultation gives them an opportunity to grow in applying a patient-tailored approach and they experienced that they were of added value. The patients appreciated the opportunity to ask their questions and share their perspectives and needs with a healthcare professional.

In several patients, problems were detected that were judged to need additional pharmaceutical or medical care. Further research is needed to explore the potential benefit of the pharmacists' consultation and the effects of this type of early intervention.

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# Appendix I

## Interview guide - patients

The questions of the interview were semi-structured, allowing interviewees to respond in their own words.

*Topic list patients - Questions relating to experiences of taking medicines:*

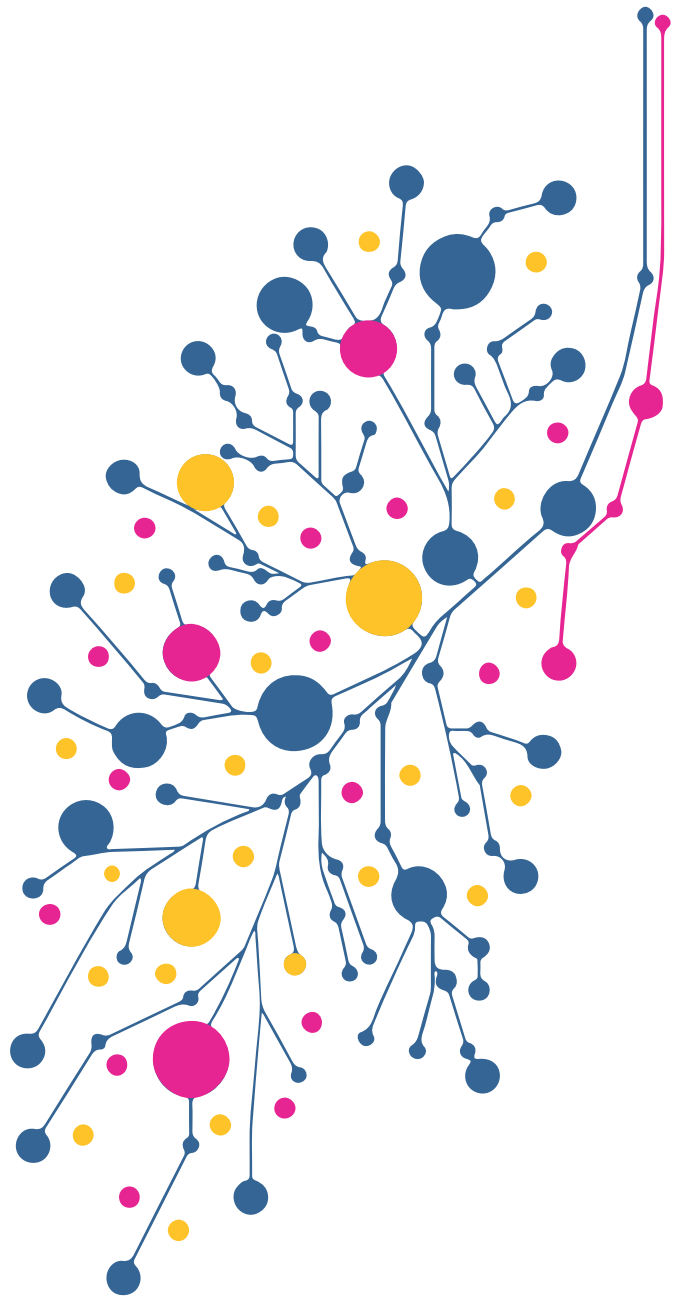
1. You have recently received new medication, what are your experiences?
2. What do you think/how do you feel about your medication?
    a. Do you believe that the medication will work?
    b. Are you worried about your medication or possible side effects?
3. Which goals do you personally want to achieve by aid of your medication to be able to do (again)?
    a. If patient indicates that he/she has no specific goal, or has never been thinking about that: now I'm asking you this, is there anything coming across your mind?
4. How do you take your medication?
    a. Are there any situations when it is easier or more difficult for you to take your medication? What tips and tricks can you share in taking your medication at theright time? Otherwise, can you explain why it is difficult for you? If applicable: What solutions have you tried?
5. Are there any advantages or disadvantages from this medication for you?
    a. If yes, which and why?
    b. How do you feel that it works?
    c. Do you experience any side-effects? If yes; which?
6. Do you have any questions regarding your medication?
7. What can I do for you?
8. How do you feel/what do you think about this conversation?

## Interview guide – pharmacists

The questions of the pharmacist interview were also semi-structured, allowing interviewees to respond in their own words.

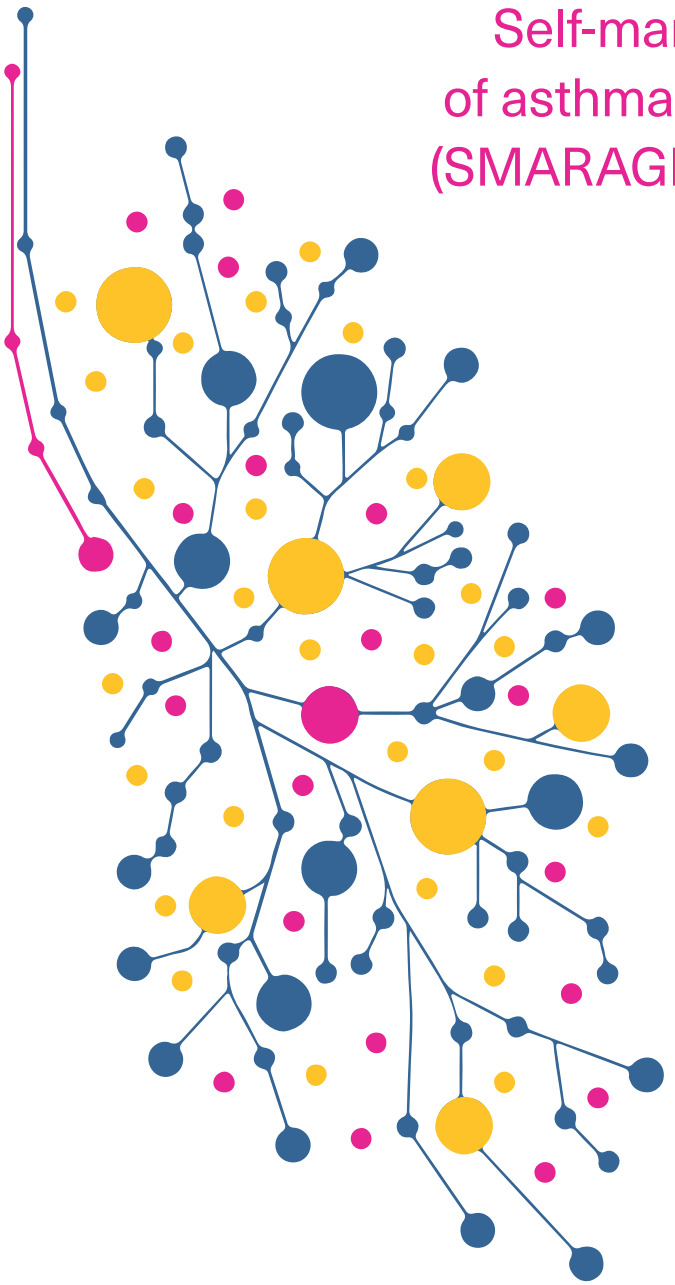
*Topic list pharmacists- experiences with the interviews*

1. What do you think about the patient interviews?
2. How did you organise the patient interviews in daily practice? (e.g. delegation of tasks, preparation, find the right moment, time investment)
3. Which interview did you enjoy or motivated you the most for future care or which conversation gave you the feeling to be of additional value as a healthcare provider? Why?



# Chapter 6

## Self-management research of asthma and good drug use (SMARAGD study): a pilot trial



Esther Kuipers, Michel Wensing, Peter AGM de Smet, Martina Teichert

*Int J Clin Pharm. 2017 Aug;39(4):888-896.*

# Abstract

## Background

Community pharmacists play an important role in supporting patients for optimal drug use.

## Objective

To assess the effectiveness of monitoring in asthma patients with inhaled corticosteroids (ICS) on disease control.

## Setting

Asthma patients using ICS were invited from two intervention (IG) and two control pharmacies (CG).

## Method

Participating patients completed questionnaires at the study start and at 6-month follow-up, including the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire. IG patients completed the CARAT questionnaire every 2 weeks and received counselling on disease management, ICS adherence, and inhalation technique when scores were suboptimal, deteriorating, or absent. For Turbuhaler users, additional electronic monitoring (EMI) was available, with daily alerts for ICS intake.

## Main outcome measure

As the primary outcome, CARAT scores at follow-up were compared between IG and CG using linear regression. As secondary outcome, refill adherence was compared using logistic regression.

## Results

From March to July 2015, we enrolled 39 IG and 41 CG patients. At follow-up, CARAT scores did not differ between IG and CG (−0.19; 95% confidence interval [CI], −2.57 to 2.20), neither did patient numbers with ICS adherence >80% (0.82; 95% CI, 0.28–2.37). Among EMI users, CARAT scores did not differ, but ICS adherence >80% showed a 4.52-fold increase (95% CI, 1.56–13.1) compared with EMI nonusers.

## Conclusion

Among community-dwelling asthma patients, pharmacist monitoring did not affect CARAT scores, but EMI use showed improved ICS refill adherence.

# Introduction

An estimated 235 million people worldwide suffer from asthma (1). Maintenance therapy with inhaled corticosteroids (ICS) has played a central role in gaining and maintaining asthma control (2). Interventions by community pharmacists reportedly improve inappropriate inhalation techniques, asthma control, patient-reported asthma-related functional status, asthma severity, and symptoms (3).

At present, pharmacists usually intervene during dispensing visits (4, 5). However, some patients may develop imperfect asthma control, and poorly adherent patients may not show up for subsequent dispensing. Timely interventions targeted at patients with suboptimal disease control may be effective in preventing exacerbations and deteriorating disease control between dispensing visits (6-8). To promote such interventions, tools are needed to continuously monitor the process of drug intake and disease control. Ideally, patients and pharmacists should cooperate in monitoring symptoms and actively manage disease control.

The available tools for prospective monitoring include questionnaires on asthma control and electronic devices measuring drug intake (9-12). One example of the former is the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire, which has been validated for disease control of asthma and allergic rhinitis (13-17). The use of medication can also be measured based on electronic monitoring of the intake of inhalation medication (EMI); that has been suggested as a well-validated means of measuring patterns of medication use (10, 11, 18). Electronic monitoring has been widely studied for many years (19-23), and it was recently shown to have a positive impact on the use of inhalation medication (10, 24).



Regular employment of the CARAT questionnaire for patient-reported monitoring and continuous utilization of EMI enable monitoring of patients' disease control and medication use. However, the usefulness of that information toward providing timely, tailored interventions in clinical practice is largely unknown. In theory, health-care providers can apply an individualized, data-driven approach for tailored interventions. For example, some patients could be helped by simplification of the dosing regimen or by practical advice linking medication intake to robust daily habits. Conversely, patients with intentional non-adherence could benefit from motivation and information about the disease, drug effects, and side effects; patients with a poor inhalation technique may benefit from improved inhaler use (7).

In this pilot study, we investigated the effects of tailored pharmacists' interventions on patients' asthma control by prospective monitoring with patient-reported CARAT scores compared with a control group receiving usual care. Secondary objectives were the effectiveness of the intervention on ICS adherence and on the number of exacerbations. All outcomes were additionally analysed with respect to the use of EMI in a planned subgroup analysis.

# Method

## Ethics approval

The study protocol was approved by the Ethical Committee of the Radboudumc Nijmegen (approval number, 2015-1569), and the trial was registered at The Netherlands National Trial Register (identifier, NTR5063). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study.

## Design and setting

This clustered controlled clinical trial was conducted between March 2015 and January 2016 in four community pharmacies in a rural area of the southern Netherlands. Dutch pharmacists have a professional and legal responsibility for the drug treatment of their patients [25]. As most patients in the Netherlands visit one community pharmacy, pharmacists usually possess the complete medication histories of their patients (26, 27, 28).

The four community pharmacies had comparable care structures: they all worked according to a certified quality management system and cooperated well with general practitioners (GPs) in structured pharmacotherapy circles (on average six GPs per pharmacy). Concealed from the patients, two pharmacies were designated as an intervention group (IG) with the intervention programme (see below). We made this choice to achieve equal practice procedures in each group. Patients in the two other pharmacies received usual pharmaceutical care–control group (CG).

## Patient inclusion

During regular pharmacy visits or by telephone, patients were invited to participate in this study when meeting the following selection criteria according to their pharmacy database: (1) age 18–60 years; and (2) current user of asthma maintenance medication. The medication included ICS or a combination of ICS and long-acting beta-agonist (LABA); the Anatomic Therapeutic Chemical (ATC) codes were R03BA, R03AK06, and R03AK07 (29), with at least two prescriptions of ICS in the previous 6 months. A current diagnosis of asthma and no (con)current chronic obstructive pulmonary disease was verified by information from the patient and the GP. Patients were included if they spoke, read, and wrote Dutch. Informed consent was obtained from all individual participants included. The follow-up lasted for 6 months after patient inclusion.

EMI could be used for inhalation medication with budesonide and formoterol (Turbuhaler) (24). The device was connected by Bluetooth® to an application on the patient's smartphone and registered every inhalation. The application was provided at no expense for the patient, and patients voluntarily shared their data with the pharmacist. Data were registered in a safe manner and provided only to the patient and pharmacist. Information on medication use became visible in the application (for up to 7 days) and a personal web portal (up to 30

days) for both the patient and pharmacist. The application reminded patients twice daily to take their medication. Both IG and CG patients were eligible for this programme if they met additional inclusion criteria: (1) at least two prescriptions of budesonide or formoterol Turbuhaler (ATC code R03AK07) (26) in the previous 6 months; (2) access to a smartphone; and (3) possessed skills to use the Internet.

## Interventions

### *Training of health-care professionals*

IG pharmacists and pharmacy assistants received additional training on asthma symptoms, treatment, possible side effects, and smoking cessation. Furthermore, they underwent 3-h training in interviewing techniques, with a focus on exploring a patient's ambivalence or readiness for behavioural change. They were also trained to give inhalation instructions and to use the CARAT questionnaire for monitoring asthma control. Pharmacists and assistants from all pharmacies received information about the EMI; however, only IG pharmacists used the monitoring information of their patients.

### *Intake and counselling session*

CG patients received standard care and checks on their inhalation technique; instructions were provided only at their own request. IG patients received an intake session as a one-to-one private counselling session with a trained pharmacist or pharmacy assistant. Depending on their needs and health literacy during those sessions, patients received tailored education on the following: asthma pathophysiology (symptoms and triggers); self-management (e.g. lifestyle advice); smoking cessation (if the patient was a current smoker); and the effects of their asthma medication. For this purpose, information from official pharmacist guidelines on asthma and patient counselling during dispensing were used (30, 31). Different elements of inhalation medication use were discussed, such as dosing and time of intake, the importance of adherence to maintenance therapy, and problems with adherence or experienced side effects and their prevention (e.g. rinsing the mouth after inhalation, good inhalation technique). In addition, the inhalation technique was checked with the patient using a demonstration inhaler unit.

### *Timely, tailored interventions based on CARAT scores*

During follow-up, the CARAT questionnaire was freely available for IG patients as a smartphone and tablet application. IG patients were instructed to download the application and received a reminder to complete and send the score every 2 weeks to the pharmacist. Via their personal e-mail, patients received graphic results of the CARAT scores they had provided; the results were presented as the scores for both domains (lower and upper airways) and the total score, and were sent by e-mail every 2 weeks. This information offered additionally self-monitoring options and insights for the IG patients.

If a CARAT score was not received within 16 days, the score signalled disease instability (total CARAT score ≤10) (15, 16), or the CARAT score deteriorated substantially (≥4 points) (15, 16), the IG pharmacist contacted IG patients by e-mail or phone to identify the reasons. According to the patient's individual situation, the pharmacist offered a tailored intervention.

For IG patients in the EMI group, the pharmacist used the EMI data to check actual drug use.

## Measures and outcomes

### *Measurement of disease control by CARAT questionnaire*

The primary outcome of the study was asthma control, measured by the CARAT questionnaire, compared between IG and CG patients. The CARAT is a 10-item questionnaire developed to measure disease control of asthma and allergic rhinitis (13-16). The first nine questions offer scores of 0 (complete absence of control) to 3 points. The last question on increased medication use the previous week has three response options ('never' = 3 points, 'less than 7 days' = 2 points, 'more than 7 days' = 0 points) and an option 'I do not take any additional medication to control my asthma,' which was also attributed 3 points. The CARAT score was calculated as the sum of the scores for all questions and ranged from 0 to 30 (14).

### *Secondary outcomes*

Secondary outcomes addressed the number of exacerbations and differences in medication adherence to ICS, measured by the Medication Adherence Report Scale (MARS-5) and by ICS refill data. Exacerbations were counted using pharmacy dispensing data of the Dutch Foundation for Pharmaceutical Statistics (SFK) (32) as well as 6 months prior to the study start and 6 months during the study period. In accordance with prevailing clinical practice guidelines, we defined an exacerbation as treatment with a course of a systemic corticosteroid (ATC codes H02AB06 and H02BA07) (29) at a dose of at least 20 mg or higher for 5–14 days (33).

IG and CG patients completed the MARS-5-questionnaire at the beginning and end of the study. The MARS-5 questionnaire is a five-item self-report measure of medication adherence for rating the frequency of different types of non-adherent behaviour (34, 35). We calculated medication adherence from ICS refill data as the proportion of days covered (PDC) by maintenance therapy with ICS (36)—whether or not in fixed combination with an LABA (ATC codes R03BA, R03AK06, R03AK07) (29)—from routinely collected dispensing data of the SFK. We calculated PDC percentages for 6 months prior to the study start and at study end for 6 months during the study period.

In a planned subgroup analysis, we additionally compared all measures between patients with and without EMI.

## Sample size

We calculated the minimal sample size for the ability to simultaneously detect a difference of 4 points (16) in CARAT scores at an assumed standard deviation (SD) of 7 and difference in medication adherence of 15% in medication possession rate (SD = 20%) between the study end and start, with 80% power at the 5% two-sided significance level. Allowing for a dropout rate of 5%, we aimed at enrolling 80 patients (13, 14).

### Statistical analysis

Using linear regression analysis, we compared the CARAT scores and mean medication adherence at follow-up between the IG and CG patients, adjusted for the subject's measurement at the study start in addition to age and sex. As neither the PDC nor the MARS-5 scores and the number of oral corticosteroid courses fulfilled the requirements for linear regression analysis (e.g. normal distribution), we used logistic regression analysis for dichotomized cut-off models, adjusted for the subject's age, sex, and status at the study start. We performed all analyses using IBM Corp SPSS statistics, Chicago IL, USA, version 23.

## Results

In the four pharmacies, 198 patients were screened for eligibility, of whom 155 (78.3%) met all the inclusion criteria (Fig. 1). In all, 80 patients (52%) agreed to participate: 41 in the CG and 39 in the IG. The two study groups were comparable regarding baseline characteristics, including type of inhaled corticosteroids (Table 1); however, the mean age of IG patients was higher than that of CG patients: 44.95 versus 39.34 years; P = 0.015. The trial was completed by 68 patients; 12 patients were lost to follow-up, largely for unknown reasons.

**Figure 1.** Flowchart participants during the study

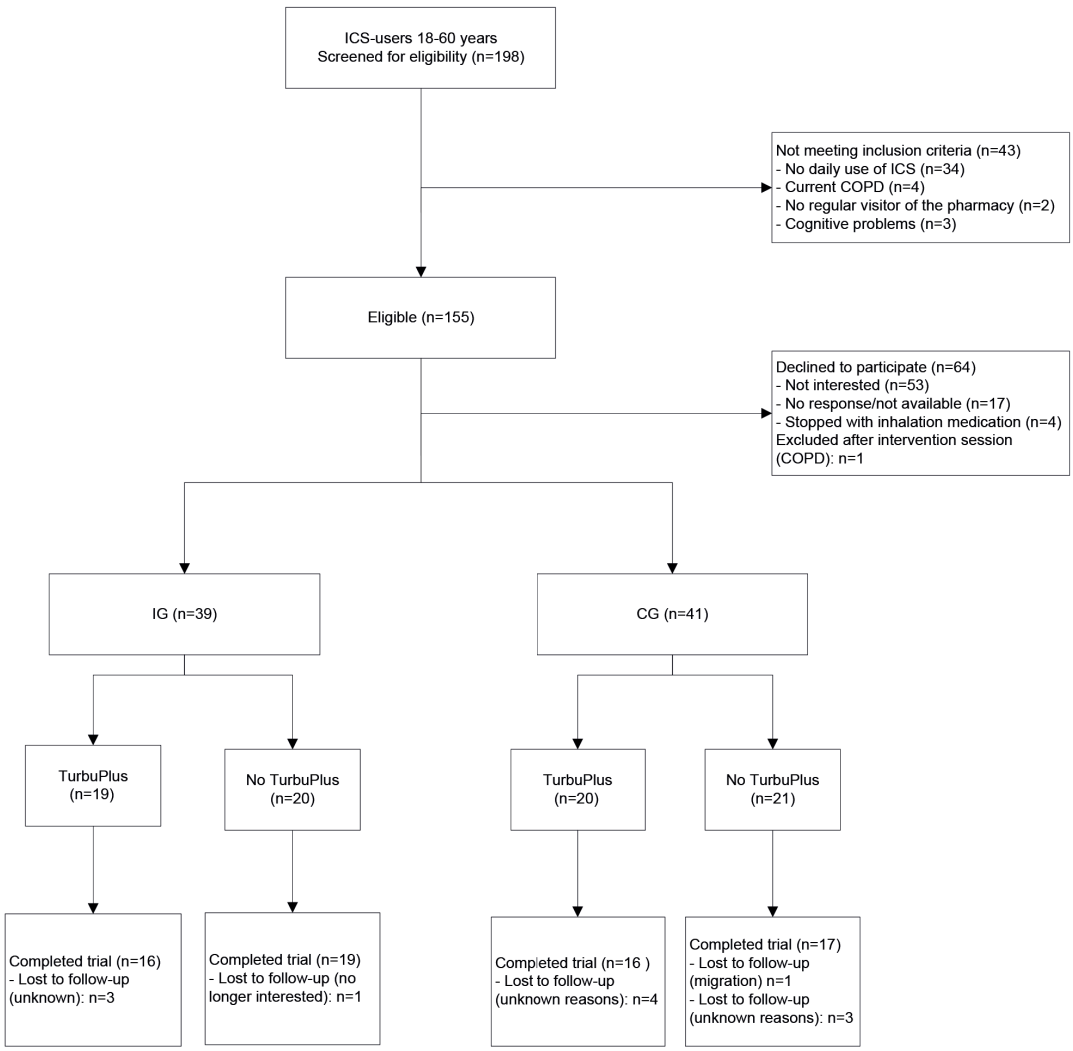


**Table 1.** Baseline characteristics

| Parameter | Intervention group (n=39) | Control group (n=41) |
|---|---|---|
| Female sex [n (%)] | 23 (59.0) | 27 (65.9) |
| Age [years; mean (SD)] | 44.95 (8.43) | 39.34 (11.48) |
| Asthma, duration [years; mean (SD)] | 23.9 (17.2) | 20.9 (14.3) |
| Number of exacerbations treated by oral corticosteroid courses 6 months before inclusion [mean (range)] | 0.13 (0; 4) | 0.02 (0; 1) |
| Smoking status: | | |
| Current [n (%)] | 9 (22.5) | 4 (9.8) |
| Earlier [n (%)] | 8 (20.0) | 12 (29.3) |
| Never [n (%)] | 22 (55.0) | 24 (58.5) |
| Electronic monitoring [n (%)] | 19 (48.7) | 20 (48.8) |
| CARAT total score [points (95% CI)] | 20.36 (17.96-22.76) | 21.29 (19.43-23.15) |
| CARAT upper airways score [points (95% CI)] | 7.46 (6.22-8.70) | 8.27 (7.26-9.27) |
| CARAT lower airways scores [points (95% CI)] | 12.90 (11.24-14.56) | 13.02 (11.74-14.31) |
| MARS-5 score [points (95% CI)] | 20.79 (19.76-21.83) | 21.22 (20.05-22.39) |
| Adherence ICS with dispensing data [% PDC (95% CI)] | 72.58 (65.46-79.70) | 84.73 (77.57-91.88) |

Among the 39 IG patients, 27 completed all 13 measurements during follow-up. Owing to deteriorating CARAT scores, 44 interventions were performed in 24 (61.5%) of the IG patients, with a maximum of four interventions for one patient (Table 2).

**Table 2.** Pharmacist interventions

| Situation | Pharmacist intervention | Frequency |
|---|---|---|
| Decreased score on CARAT-domain upper airways | Inquire about actual hay fever complaints and recommended the use of oral, ocular or nasal antihistamines or nasal corticosteroids | 32 times |
| Low adherence scores | Tailored advice to eventual barriers to chronic drug use or fear of ICS side effects or to patients' poor knowledge of asthma disease. Discuss the importance of medication adherence. | 4 times |
| CARAT-score decreased substantially, possible overuse of short acting beta agonists (SABA, use of ≥3 times a week) | Contact with patient to explore actual symptoms and possible reasons. Invitation for visiting the pharmacy for a check of the inhalation technique. Contact with prescriber to discuss switch of medication (e.g. another nasal corticosteroid) | 4 times |
| Persisting symptoms, despite interventions and adherent use of ICS | Referral to the general practitioner for evaluation of persisting symptoms. | 2 times |
| CARAT-score ≤10; indicating a possible exacerbation | Referral to the general practitioner for examination of a possible exacerbation and prescription of rescue medication, if needed. | 2 times |

At baseline, the mean CARAT scores were comparable between the IG (20.36 points) and CG (21.29 points). In multivariate regression analysis, the total CARAT scores at follow-up did not differ between the IG and CG (Table 3): mean estimated difference, −0.19 for the total score; 95% confidence interval (CI), −2.57 to 2.20). Likewise, the CARAT scores for the upper airways (−0.22; 95% CI, −1.01 to 1.44) and lower airways (−0.62; 95% CI, −2.30 to 1.06) did not vary. We observed no difference between the groups for the outcomes for medication adherence: the probability of having a period covered by drug use >80% did not vary between IG and CG (Odds Ratio, OR 0.82; 95% CI, 0.28–2.37).

**Table 3.** Differences in outcome measures between intervention and control group at follow up

| Outcome measure | Difference |
|---|---|
| CARAT total score (95% CI)# | -0.19 (-2.57 – 2.20) # |
| CARAT upper airways score (95% CI)# | 0.22 (-1.01 – 1.44) |
| CARAT lower airways scores (95% CI)# | -0.62 (-2.30 – 1.06) |
| Period covered by drug dispensings >80% (95% CI) & | 0.82 (0.28 – 2.37 |
| MARS-5 score >20 (95% CI) & | 0.55 (0.15 – 2.05) |
| At least one oral corticosteroid short course & | No corticosteroid short courses in control group |

# linear regression analysis, adjusted for age, sex and baseline score, CI = Confidence Interval
& logistic regression analysis, adjusted for age, sex and baseline score

The probability of achieving a score >20 on the MARS-5 questionnaire (28) at the study end did not differ between the two groups (0.55; 95% CI, 0.15–2.05). Finally, no differences between IG and CG were found for the number of exacerbations, measured by oral corticoid courses.

A planned subgroup analysis was performed for the 39 patients with EMI compared with the 41 without EMI. Those groups did not differ in terms of baseline characteristics, except for a higher mean age of EMI patients: 44.08 years versus 40.17 years; P = 0.001 (Table 4). In the EMI subgroup, refill adherence >80% showed a 4.52-fold increase: 95% CI, 1.56–13.1 compared with no EMI use. We observed no differences among the other measures (Table 5).

**Table 4.** Baseline characteristics for subgroups with and without EMI

| Parameter | EMI-group (n=39) | No EMI- group (n=41) |
|---|---|---|
| Female sex [n (%)] | 21 (53.8) | 29 (70.1) |
| Age [years; mean (SD)] | 44.08 (6.93) | 40.17 (12.71) |
| Asthma, duration [years; mean (SD)] | 23.50 (15.49) | 21.32 (16.20) |
| Number of exacerbations treated by oral corticosteroid courses 6 months before inclusion [mean (range)] | 0.10 (0-2) | 0.12 (0-1) |
| CARAT total score [points (95% CI)] | 20.95 (18.62-23.27) | 20.73 (18.78-22.68) |
| CARAT upper airways score [points (95% CI)] | 8.00 (6.81-9.19) | 7.76 (6.68-8.83) |
| CARAT lower airways scores [points (95% CI)] | 12.95 (11.38-14.51) | 12.98 (11.59-14.36) |
| MARS-5 score [points (95% CI)] | 21.08 (19.97-22.18) | 20.95 (19.84-22.06) |
| Adherence ICS with dispensing data [% PDC (95% CI)] | 82.38 (75.47-89.28) | 75.42 (67.74-83.08) |

**Table 5.** Differences in outcome measures compared between patients with and without electronic monitoring device at follow up

| Outcome measure | Difference |
|---|---|
| CARAT total score (95% CI)# | 1.49 (-0.82 – 3.80) |
| CARAT upper airways score (95% CI)# | 0.95 (-0.20 – 2.10) |
| CARAT lower airways scores (95% CI)# | 0.52 (-1.12 – 2.17) |
| Period covered by drug dispensing >80% (95% CI)& | **4.52 (1.56 – 13.1)** |
| MARS-5 score >20 (95% CI)& | 2.13 (0.60 – 7.55) |
| At least one oral corticosteroid short course & | 3.40 (0.25 – 46.50) |

statistically significant outcomes are printed in bold
# linear regression analysis, adjusted for age, sex and baseline score
& logistic regression analysis, adjusted for age, sex and baseline score

# Discussion

In this study, we found that additional timely, tailored pharmacist interventions did not increase asthma control or ICS adherence compared with usual care. With EMI, we recorded effects on refill adherence but not on the CARAT or MARS-5 scores.

Though at first sight these results appear disappointing, a number of mitigating considerations exist. First, this investigation was established as a pilot study to determine the usefulness and feasibility of patient-reported monitoring in measuring asthma control over time. Some studies have investigated community pharmacist interventions to improve asthma control; however, disease control was mainly assessed using the Asthma Control

Questionnaire or Asthma Control Test, not the CARAT questionnaire (2, 3). The number of eligible patients willing to participate in the present study was just sufficient to detect a difference in CARAT scores of 4 points between the study groups; that is considered a clinically relevant score, according to the CARAT developers (16). At baseline, little was known about the CARAT scores of community-dwelling asthma patients in primary care. Our study showed high CARAT scores—an average of 21 points—for this population at study start. Hitherto, CARAT scores have been measured monthly, and little has been known about their development over time. The measurement of CARAT scores every 2 weeks was feasible in the IG and enabled regular pharmacist-patient contacts between dispensing visits.

In the planned subgroup analysis for EMI, ICS refill adherence >80% was 4.52-fold (95% CI, 1.56–13.1) that of EMI non-users. When including only subjects with CARAT scores below 23 points at the study start, the OR of achieving higher CARAT scores at the study end was 2.87 (95% CI 0.61–13.6) for the EMI group compared with the non-EMI group. This finding suggests that poor asthma control due to underuse of maintenance therapy with ICS may be improved more effectively in this population by EMI than with a tailored pharmacist intervention. Regarding the difficulty in demonstrating the effects of tailored interventions on disease outcomes, the findings of the present study are not unique: a recent investigation about tailored counselling on health-related lifestyles in cardiovascular diseases also reported no effect on the primary outcome (37). This suggests that for asthma patients in primary care, EMI may be sufficient for improving medication adherence; however, the effects on disease outcomes remain to be shown. Furthermore, selection bias cannot be fully excluded in the present study as patients voluntarily participated in the study and for EMI use if suitable. In general however, in the Netherlands all inhabitants are obliged to have a health care insurance, which gives access to all asthma medications. Therefore we do not expect selection bias from this cause for our findings.

The absence of spirometric confirmation of the asthma diagnosis could be considered a limitation. However, pharmacists do not generally have access to such data. Corresponding with clinical practice, an asthma diagnosis was initially assumed from the use of asthma medication; it was verified with the patient and information from the registration of contraindications in the computer system of the GP, if available. We did not dispose of information on comorbidities. Although asthma patients included were relatively young and patients' age was comparable between the groups, we cannot fully exclude that we might have missed differences between the groups due to comorbidity. With regard to exacerbations, the use of short-term corticosteroid courses was low in both groups. A sub-analysis with pooled measures of both types of short-term courses did not achieve statistical significance. Finally, the use of EMI within both IG and CG groups may have influenced our intervention. However, in further analysis, we did not observe any interaction between the intervention and EMI use (P = 0.11 for a multiplicative interaction term).

## Conclusion

Our results did not show an effect of tailored pharmacist interventions on patient-reported disease control in a general asthma population compared with usual care. To support non-intentional non-adherence in this population, EMI may be effective; however, that strategy needs to be confirmed with greater patient numbers for a longer follow-up period for clinical outcomes.

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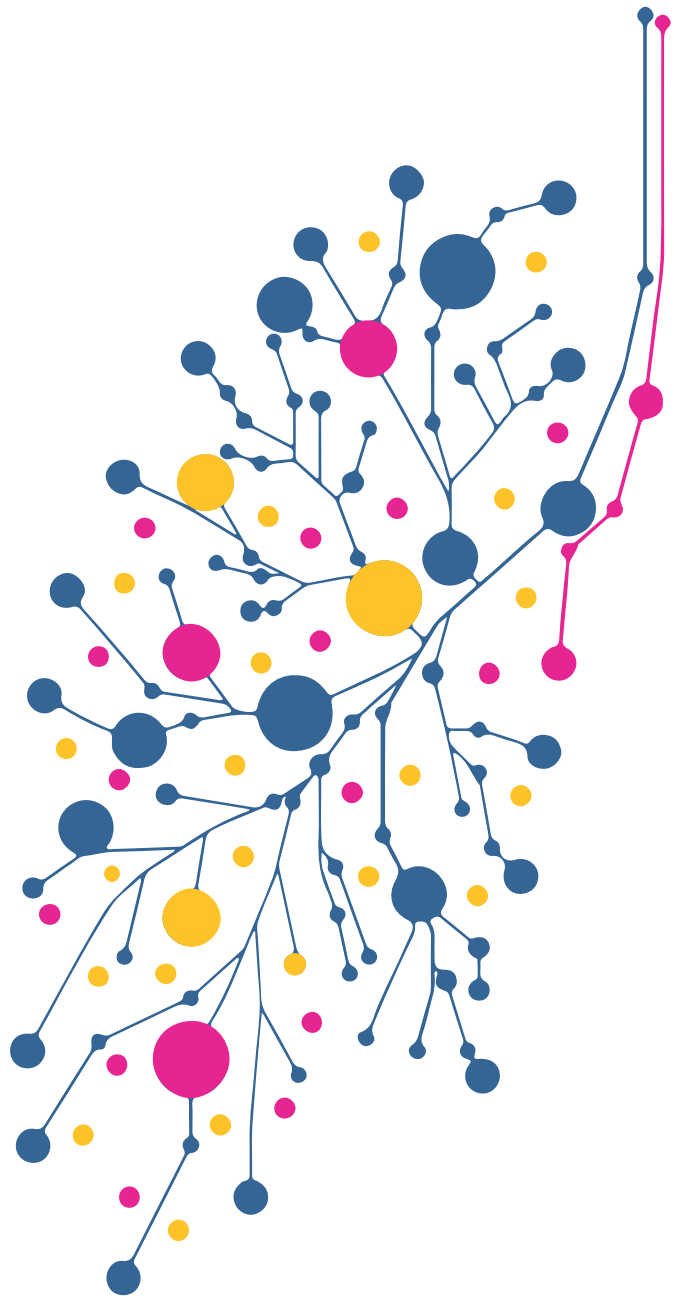
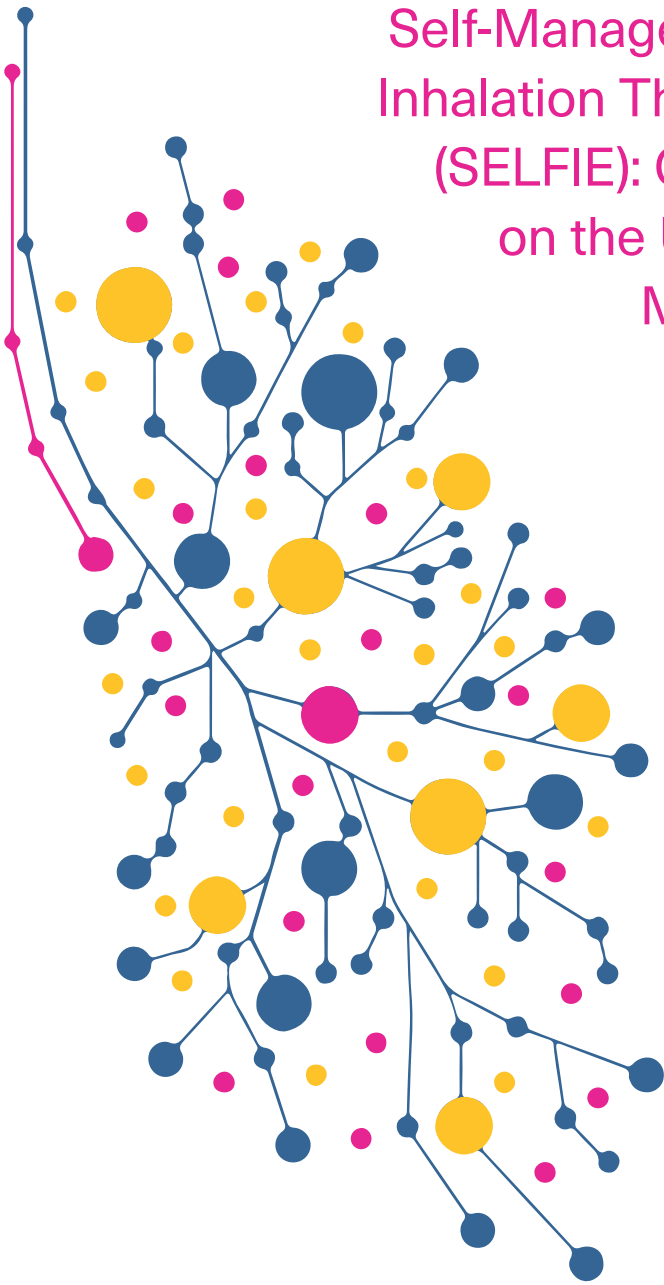


# Chapter 7

## Self-Management Maintenance Inhalation Therapy With eHealth (SELFIE): Observational Study on the Use of an Electronic Monitoring Device in Respiratory Patient Care and Research



Esther Kuipers, Charlotte C Poot, Michel Wensing, Niels H Chavannes, Peter AGM De Smet, Martina Teichert

*J Med Internet Res. 2019 May 30;21(5):e13551.*

# Abstract

## Background

Electronic inhalation monitoring devices (EIMDs) are available to remind patients with respiratory diseases to take their medication and register inhalations for feedback to patients and health care providers as well as for data collection in research settings.

## Objectives

This study aimed to assess the validity as well as the patient-reported usability and acceptability of an EIMD.

## Methods

This observational study was planned in 21 community pharmacies in the Netherlands. Patient-reported inhalations were collected and compared to EIMD registrations to evaluate the positive predictive value of these registrations as actual patient inhalations. Patients received questionnaires on their experiences and acceptance.

## Results

A convenience sample of 32 patients was included from across 18 pharmacies, and 932 medication doses were validated. Of these, 796 registrations matched with patient-reported use (true positive, 85.4%), and 33 inhalation registrations did not match with patient-reported use (false positive, 3.5%). The positive predictive value was 96.0%, and 103 patient-reported inhalations were not recorded in the database (false negative, 11.1%). Overall, patients considered the EIMD to be acceptable and easy to use, but many hesitated to continue its use. Reminders and motivational messages were not appreciated by all users, and more user-tailored features in the app were desired.

## Conclusions

Patients' interaction with the device in real-world settings is critical for objective measurement of medication adherence. The positive predictive value of this EIMD was found to be acceptable. However, patients reported false-negative registrations and a desire inclusion of more user tailored features to increase the usability and acceptability of the EIMD.

# Introduction

Electronic monitoring devices are increasingly important in the self-management of chronic diseases such as chronic obstructive pulmonary disease and asthma. These two chronic respiratory diseases affect an estimated 384 and 235 million people worldwide, respectively (1,2). According to the prevailing clinical guidelines, daily intake of inhaled corticosteroids is the cornerstone for optimal asthma treatment, and inhaled corticosteroids are also utilized in chronic obstructive pulmonary disease, together with bronchodilators (2,3).

An electronic inhalation monitoring device (EIMD), which measures inhalation actuations, provides detailed data on patient adherence to treatment to both patient and health care providers (4-7). EIMDs, in combination with audiovisual reminders and feedback, have the potential to improve medication adherence and health care outcomes by facilitating self-management and aiding in clinical (shared) decision making (8-15). Previous studies have shown that involving patients in monitoring their own symptoms can lead to improved awareness and competence in disease management (16).

Besides clinical practice, EIMD data could be used as objective outcome measures for medication adherence in research (17-19). The integrated time stamp enables comprehensive data collection in research populations on the timing and pattern of inhaler actuation, including dose dumping (20). This way of data collection was stated to be more accurate and objective for the evaluation of medication use and is considered to be superior to self-report, canister weighing, or pharmacy dispensing data (17,21).

However, the widespread use of EIMDs for measuring patients' medication adherence in clinical practice and research setting depends on the acceptability by patients as well as health care providers and researchers, respectively. From the perspectives of both patient care and research, it is important that the EIMD is accurate and valid (20,22-24). Earlier in-vitro studies (product validation studies) evaluating the validity of an EIMD, following a fixed protocol and simulating inhalations, found 99.2% overall accuracy of detection (25). On the contrary, small-scale studies reported malfunctioning devices and potential loss of data as well as overrecording of doses that did not reflect actual inhalations (22-24,26). Use of EIMDs as objective measures for medication adherence for research purposes in a real-world setting depends not only on technical capabilities, but also on how the user interacts with the system in real life. In other words, results in laboratory settings might not apply to EIMD validity and reliability in the broad use by community-dwelling patients. As EIMDs could be used for measuring real-time medication adherence in clinical trials, evidence on their potential to measure patient inhalations in community-dwelling patients is relevant.

For the implementation of EIMD in clinical practice, it is important to acknowledge the complexity of the implementation process, influenced by patients' acceptance and ability to use information technology tools (27,28). Hence, before the EIMD is implemented and used as an accurate and reliable measure for patients' actual medication adherence in a

real-world setting (in both clinical decision making and research), a rigorous evaluation of the technical performance, usability, and acceptability in clinical practice is required.

This study aimed to assess the validity and patient-reported usability and acceptability of an electronic adherence monitor and reminder device for patient care and research.

# Methods

## Study Design

This prospective observational study on agreement between EIMD measurements and patient-reported inhalations was conducted between April 18 and May 25, 2018.

## Setting

This study was conducted by 21 students in the second year of their master's program in pharmacy from the University of Leiden, the Netherlands, during their internships in community pharmacies. The students were asked to validate EIMD registrations for two patients each, for 3 weeks, and they received additional training on the use of the EIMD program. The individual monitoring of patients was time consuming because of the protocol-specific information requirements, and consequently, dedicated persons with enough time were needed in the pharmacy. Additionally, the acquaintance with an innovative device to be implemented into daily practice and individual patient coaching were relevant learning objectives for the students.

Dutch pharmacists have a professional and legal responsibility to provide drug treatment for their patients and, as most patients in the Netherlands attend one community pharmacy, pharmacists usually possess the complete medication histories of their patients (29).

## Ethics Approval

The study protocol was approved by the Ethical Committee of the Radboudumc Nijmegen (approval number, 2018-4153). Written informed consent was obtained from all individual participants included in this study, prior to the study.

## Electronic Monitoring

The EIMD to be assessed was the Turbu+ V2.1 (AstraZeneca UK Limited), consisting of three components: (1) the electronic device that could be attached to the inhaler of the corresponding product "Symbicort Turbuhaler," (2) an app to be installed on the patient's mobile phone, and (3) an online portal allowing the health care professional access to the same actuation data. During patient inhalation, the device was actuated and the date and time of the actuations were recorded. The data were synchronized with the app on the mobile phone by Bluetooth, and the app visualized the timeline of these data up to the previous month. All EIMD data for measured actuations were automatically and electronically linked to the online portal of the health care provider for his/her patients and an additional research database containing the same data anonymized. The research

database has been setup to study patterns of medication adherence and to evaluate the effectiveness on interventions for medication adherence across multiple studies. Actuation data from all health care professionals included in this study were aggregated into one central research database containing data on all included patients from the participating pharmacies.

Patients could only use the EIMD program after they were enrolled and trained by their health care provider. After entering the name, birth of date, sex, dose regimen settings, and email address, the patient automatically received an email with the link to download the app. The time(s) for a pop-up reminder in the app could be set individually by the patient at the time of scheduled inhalation(s). If patients did not take their medication, 30 minutes after the scheduled inhalation, a "missed-medication" motivational message was sent automatically. Patients received a weekly motivational push notification in the app (eg, "Great week. You've been following your prescription this week! Keep it up!").

## Patient Inclusion

Patients were eligible to participate if they (1) were current users of budesonide/formoterol Turbuhaler (Anatomic Therapeutic Chemical code R03AK07) (30) with at least two prescriptions in the previous 12 months; (2) were of age ≥18 years; (3) were regular patients in the pharmacy (registered in the pharmacy system and receiving dispensings from this pharmacy only); (4) had access to a smartphone, and (5) were able to use the internet. We aimed to include current users who were familiar with the inhaler. At random, eligible patients were invited during regular pharmacy visits or by phone. If interested, patients received an information leaflet on the study and an informed consent form. Patients interested in participating were asked to provide informed consent, allowing the student to collect general data about gender, age, use of short corticosteroid courses (indicating exacerbations), and refills from the pharmacy database (to assess adherence rates). Eligible patients were invited to the pharmacy for an intake visit.



## Intake Visit

During the intake visit, the students provided the patient with an EIMD and (oral and written) instructions. The patients attached the device to the inhaler and installed the app during the visit or at home following the instructions. Additionally, the students verified the pharmacy's information collected on drug use, patient's refill adherence to inhaled corticosteroids, and the number of oral corticosteroid courses in the previous year. Subsequently, the patients completed the Beliefs about Medicines Questionnaire (BMQ), consisting of two parts: the BMQ Specific list, which measures perceptions of specific medicines, and the BMQ General list, which measures general beliefs about medicines. The BMQ Specific list comprises two scales—one assessing patients' beliefs about the necessity of preventer medication for maintaining present and future health (Necessity scale) and the other for assessing their concerns about the potential adverse consequences of using such medication (Concerns scale) (31,32). All items were rated on a 5-point Likert scale, with a range of 5-25 possible scores for both scales.

The students explained that they would call the patients 6 times within 14-21 days to check on their actual drug intake on the previous days and agreed on the most suitable days and time to call. If patients wished to, they were allowed to use a paper diary.

## Electronic Inhalation Monitoring Device Accuracy Versus Patient-Reported Use: Procedures and Measures

During the follow-up period of 14-21 days, the students phoned the patients 6 times to check on their actual drug intake and EIMD performance from the previous day, and if possible, up to the day of the earlier phone call. The student collected and reported information on the number and time of daily inhalations, and all particularities or other circumstances that the patient reported were registered by the student in an Excel file. These were subsequently centralized into one patient self-reported database.

To avoid socially desirable answers and collect reliable data, patients were instructed that this study focused on the accuracy of the device (instead of their medication use), and they were asked to use the medication at their usual dose and frequency and to use only the EIMD prepared device during the study period and no other inhalers of this medication. Semistructured questions were used during the phone call; for example, “When did you use your medication for the last time?” and “Do you see any registrations in your app that do not represent real medication use?” During the phone call, the student had immediate access to the EIMD data and compared the data from the research database with the information reported by the patient (and registered in the patient self-reported database). Any discrepancies were directly discussed with the patient and registered.

## Patient Electronic Inhalation Monitoring Device Usability and Acceptability: Procedures and Measures

To evaluate patients’ usability, patients received two questionnaires at the end of the study, including the System Usability Scale (SUS), which is a validated instrument for evaluating the usability of a wide range of products and services (33,34). The SUS score can range from 0 to 100. For products with a score less than 70, improvement options should be considered (34).

The second questionnaire addressed the experiences and acceptability of the program and the expectations on the pharmacists’ role in counselling. This part consisted of 12 statements, formulated positively or negatively, measured on a 5-point Likert Scale (1=strongly disagree, 5=strongly agree), followed by 3 multiple-choice questions regarding the frequency of using the app and whether the patient would like to continue the program and by 4 open questions on advantages, disadvantages, and targets for improvements.

## Data Analysis

The main outcome measure was the positive predictive value (PPV), calculated as (the number of correctly registered doses according to the patient self-reported database and registered database)/(the total number of registered doses [true and false positives])*100. Results of the questionnaires were analyzed using descriptive statistics. Responses to the

open questions were coded and summarized for patients' opinions, wishes, and barriers encountered using the EIMD program to identify key topics via the grounded theory approach (35).

Patient-specific characteristics were assessed with the scores for the BMQ Specific and BMQ General questionnaires, represented on a continuous scale. The BMQ necessity and concerns scores were split at the scale midpoints to distinguish between four subgroups: accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), skeptical (low necessity, high concerns), and indifferent (low necessity, low concerns) (36). Refill adherence was calculated as the proportion of days covered in the prior 12 months (due to prior dispensings up to 15 months).

# Results

## Patient Demographics and Questionnaire Completion

A total of 32 patients were included by 18 students (Table 1). In 3 pharmacies, no patients eligible and willing to participate were available. The mean age of the included patients was 48.1 years (range, 20-69 years), and 17 patients were female (53.1%). Medication adherence in the previous year calculated from dispensing data was 81.3%. Most patients used their medication twice a day (n=26). Three patients (9%) used an additional diary to note their daily inhalations. Twenty-five patients (78%) completed the questionnaires and provided individual comments on the EIMD (Table 2 and Textbox 1).

Thirty patients (94%) completed the BMQ General and Specific questionnaires at the start of the study. The majority of them could be classified as acceptant (n=19) regarding their inhalation medication; 4 patients were ambivalent, and 7 were indifferent. No patients were classified as skeptical.



**Table 1.** Patient characteristics (N=32).

| Characteristic | Value |
|---|---|
| Age (years), mean (range) | 48.1 (20-69) |
| Female, n (%) | 17 (53.1) |
| Number of oral corticosteroid courses in the last year, mean (range) | 0.31 (0-4) |
| Medication adherence in the previous year calculated from dispensing data (n=28), mean % (range) | 81.32 (17.53-194.80) |
| BMQ General Harm score (n=29; possible range: 4-20), mean (range) | 10.21 (5-16) |
| BMQ General Overuse score (n=29; possible range: 4-20), mean (range) | 8.04 (4-13) |
| BMQ Specific Necessity score (n=30; possible range: 5-25), mean (range) | 17.70 (10-24) |
| BMQ Specific Concerns score (n=30; possible range: 5-25), mean (range) | 10.97 (6-17) |

## Electronic Inhalation Monitoring Device Accuracy Versus Patient-Reported Use

Of the 32 patients, 28 completed all 6 phone calls. Overall, the 18 students verified 932 medication doses (mean=29.1 doses verified per patient; range=3-88). A total of 796 doses registered in the research database matched patient-reported inhalations captured in the patient self-reported database (true positive, 85.41%). In addition, 33 inhalations were registered in the research database that did not match actual drug intake, as reported by the patients in the patient self-reported database (false positive, 3.5%). Further, 22 patients reported an average of 4.7 inhalations (range, 1-20) that were not recorded in the research database, accounting for a total of 103 inhalations (false negative, 11.1%).

Information on registration of 6 of the 32 devices was in full agreement with the patient-reported inhalations. The PPV of all registrations in the research database was 96.0%. Some patients reported technical problems with EIMD data recording and synchronization of the EIMD data with their mobile phone. Delayed data synchronization resulted in two patients taking more medication than prescribed under the assumption that they had forgotten their dose.

## Electronic Inhalation Monitoring Device Usability and Acceptability

The majority of patients indicated that the app was easy to use and not unnecessarily complex; the mean SUS score was 68.9 (SD 11.34; range, 52.5-90).

In the acceptability questionnaire, patients rated the EIMD generally as useful (76% neutral or agree) and 84% rated the EIMD program as not time-consuming (Table 2). With regard to recommending the EIMD to other patients, the majority rated this item as neutral (n=12, 48%). In addition, 80% of the patients indicated that they were not willing (n=15) or uncertain ("maybe", n=5) about continuing the program themselves, and 70% (n=14) of these patients reported that they had only participated in this study because they wanted to help the students fulfil their assignment and facilitate the research. The five patients who were positive about continuation reported that they participated mainly to gain personal insight into their inhalation patterns. The patients generally felt positive about the pharmacists' role in counselling.

Written feedback on the advantages, disadvantages, and targets for improvements was provided by 25 patients. This feedback was clustered into four themes: EIMD functionality, reminders, motivational messages, and attitude toward electronic monitoring (Textbox 1).

Some of the previously mentioned technical issues reported by some patients resulted in a level of frustration or confusion because of missed or unnecessary reminders due to missing data, which impacted their acceptance of the app (Textbox 1). The reminders and motivational messages were appreciated by 9 and 4 patients, respectively. Several patients suggested more individualization of the settings in the app, such as inclusion of a personal choice to share data with a specific health care provider and management of their dose regimen settings.

**Table 2.** Patients' acceptability of Electronic Inhalation Monitoring Device program.

| Question | Disagree (score 1-2), n (%) | Neutral (score 3), n (%) | Agree (score 4-5), n (%) |
|---|---|---|---|
| The EIMD programme does provide useful insights in my medication use[a] | *11 (44)* | 3 (12) | *11 (44)* |
| The EIMD programme is useful to me | 6 (24) | 8 (32) | *11 (44)* |
| The EIMD programme is time-consuming | *19 (76)* | 2 (8) | 4 (16) |
| The motivational messages in the EIMD app feel positive for me | *11 (44)* | 10 (40) | 4 (16) |
| The reminders of the EIMD programme help me to take my medication in time | *10 (40)* | 6 (24) | 9 (36) |
| The EIMD programme contributes to dealing with my illness[a] | *10 (40)* | 5 (20) | *10 (40)* |
| The EIMD programme contributes to the interaction with my pharmacist | *10 (40)* | 8 (32) | 7 (28) |
| The EIMD programme helps establishing a habit to use my medication | *11 (44)* | 9 (36) | 5 (20) |
| The EIMD programme gives me confidence to help manage my disease | *10 (40)* | 9 (36) | 6 (24) |
| The pharmacist's monitoring of my medication use with this programme helps me to use my medication better[a] | *13 (52)* | 6 (24) | 6 (24) |
| When someone can monitor my medication intake, I take my medication as usual[a] | 4 (16) | 3 (12) | *18 (72)* |
| I see added value of the EIMD programme to manage my medication intake[a] | *11 (44)* | 5 (20) | 9 (36) |
| I would recommend the EIMD programme to other patients | 7 (28) | *12 (48)* | 6 (24) |
| The pharmacist can play an important role in counselling | 2 (8) | 3 (12) | *20 (80)* |

Values in italics indicate the highest percentage(s) per statement.
[a]Item was phrased as a negative statement.

**Textbox 1.** Selection of patients' free-text comments about the Electronic Inhalation Monitoring Device program. Values in brackets represent gender and age of the participants (eg, F24=female, 24 years).

**Technical functionalities:**

*If the app synchronises the data, this may take a long time (maybe this can be improved). In the end, the registration of my puffs did not go well.* [F24]

*Until now, the app missed three inhalation registrations in the morning. I clicked twice within a minute, but only one [inhalation] was registered.* [M52]

**Patient-technology interaction:**

*Not all inhalations were registered [in the app on my mobile phone], so I inhaled again and used too much medication.* [F45]

*The app is not always working. If medication is taken, this is not always measured. Even if the medication has already been taken (before the time set), still a reminder was sent. The app does not provide insight into whether the medication has been taken in the right way.* [F20]

*The alarm you can set will never go off. So you have no reminder.* [F45]

*The Turbu+ did not register when the app was [physically] not around, and it was therefore not possible to register 2 inhalations in 1 day.* [M55]

*The notifications did not work with my Galaxy s7 Edge.* [M57]

**Patients' opinions and acceptability of the program:**

Regarding the device/app:
*The device itself feels rather rickety. The two parts did not really fit together.* [M51]

*The idea is good, I also see the commercial need, but think about the return for the patient. Information in the app for how many days medication is still available in the inhaler, would be such convenient return for the patient. For example, before he goes on holiday, he knows if there are extra medicines needed.* [M55]

*I feel that tracking medication use can be useful for many patients. However, it remains very difficult, because the connection of the device and the app is not clear. As a result, it [medication use] is registered at some time, but not on other times, for unclear reasons. With this, possible useful options of the app will immediately disappear.* [M43]

Regarding reminders:
*If you are not adherent, the Turbu+ can be convenient as a reminder for using the medication.* [F39]

*[Useful] when you forget [medication intake] (but I never forget this).* [M42]

*I personally liked the reminders, and it was also very pleasant that I could monitor myself whether I had taken it or not!* [F24]

**Textbox 1.** Continued.

| |
|---|
| *I would like to modify the app myself for what I agreed on with my doctor (about minimum and maximum use per day).* [F47] |
| *[I would prefer] a clearer reminder sound signal.* [V56] |
| Regarding motivational messages:<br>*The tone of the written messages deserves carefulness: the patient is the boss, the app only gives advice.* [F47] |
| Regarding attitude to electronic monitoring:<br>*I would only use the app if only I can see it [the data]. Watching by pharmacist should not be the default for each patient.* [F47] |
| *I am intrinsically motivated to use my medication and do not really need an app for that.* [M55]<br>*Once the routine is there to take an inhalation twice a day, it has little added value for the users. It gives the impression that it is only useful for the pharmacist and the manufacturer to collect Big Data.* [M55] |
| *I always take my medication when brushing my teeth. So there was no need for help with the intake. In addition, I am able to feel when I have to use my medication more often, according to my needs. I think that the app can help people who have difficulties with this.* [M28] |
| *[An advantage is] to check when I am not sure about forgotten medicines. Insights into patterns in periods when I have more symptoms help me to anticipate.* [F48] |

# Discussion

## Principal Findings

In this study, we found an acceptable PPV: 96.0% of the registered doses represented patient-reported drug intake. However, we found a high number of false-negative registrations: 11.1% of patient-reported inhalations were not recorded by the EIMD.

These unrecorded patient-reported inhalations could have been the result of a number of factors, either technical or user-related issues, that should be discussed. Although in earlier studies, loss of data or missing data were associated with technical issues such as battery drain, this was not likely to have occurred during the short duration of our study (7,24,26). The high number of false-negative registrations could possibly be the result of overreporting by the patients or suboptimal use of the device (e.g., Bluetooth not activated, EIMD not paired to the phone, or EIMD not within a 5-meter distance from the phone during inhaler actuation). Assessment of user experience revealed that the written instruction did not contain detailed information about the data synchronization protocol, which, combined with instructions at enrolment, may have led to some of the reported observations. In earlier research with the same EIMD, the researchers had presumed the possibility of false-negative as well as false-positive registrations, but they were unable to verify the

registrations by patients' actual inhalations or the data on user interaction with the system to interpret their findings (15).

This study demonstrated the importance of validating medication adherence data in real-world settings. Patients' interaction with the device is critical for objective measurement of medication adherence in research and clinical settings. We emphasized on the importance of evaluating technical performance to identify technical/user issues and stressed the need of evaluating usability and acceptability across multiple components of the EIMD.

Previous studies on EIMD performance focused on accuracy and reliability in laboratory settings and lacked data collected in a real-life setting where patients interact with the EIMD. Furthermore, previous studies did not access patient acceptability and user experience (7,20,23,24,26,37,38), both of which are essential for successful implementation and sustained use in daily practice (39). This is the first study to demonstrate the importance of evaluating and validating EIMDs in a real-world setting. The accuracy of inhalation measurement is essential from not only a research point of view, but also a clinical perspective, as false-negative registrations lead to unnecessary signals and reminder messages. Furthermore, it falsely reports patients as not adherent, and this could lead to underestimation of adherence, incorrect clinical decision making, and overuse of medication when patients assume to have forgotten their dose.

## Electronic Inhalation Monitoring Device Patient Experiences and Acceptability

Our findings on acceptability and user experiences further underline the importance of evaluating EIMDs on acceptability, preferably early in the implementation process. There is a growing body of evidence on electronic health apps, in general, that do not perform as expected in clinical practice, because the app turns out to be unacceptable or does not fit the users' needs (40-43). Although patients indicated that the app was easy to use and not complex, the majority did not intend to use the app in the future, apparently because there was no clear personal need to use the EIMD. They were primarily motivated to use the EIMD to facilitate the research rather than having an intrinsic motivation to gain personal insights into their inhalation patterns, and their medication adherence in the previous year calculated from dispensing data was already high. Patients with intrinsic motivation to improve their disease management (eg, based on low adherence or impaired disease control) would possibly benefit more from the EIMD. Therefore, understanding different types of patient segments is important to succeed in the implementation; the EIMD needs to match with the patient profile (eg, adherence and asthma control), needs, and preferences.

In addition, the fact that the majority of patients did not intend to continue with the EIMD may have been the result of a suboptimal technical performance, for example, loss or troubles with the Bluetooth connection, which was regularly experienced; delay in the synchronization of data from the EIMD to the mobile app; and inhalations taken just before midnight were not visible on the intended day. These technicalities can probably easily be improved and thereby increase the chance of acceptance and successful implementation.

Moreover, health care providers and patients would benefit from further development of the EIMD, so that it can not only detect inhaler actuation, but also check the inhalation quality, breath force, and inhalation technique.

Our findings emphasized the need for clear patient selection and a more individualized, tailored device. In this study, half of the people found the reminders helpful in taking the medication on time, while the other half found them useless. We found similar results for the motivational messages. Hence, when designing a self-management intervention containing multiple self-management strategies (ie, motivational messaging, reminders, and audio-visual behavioral feedback), it is important to critically review each component on usability separately and preferably tailor the intervention to the needs of the patient.

## Strengths and Limitations

This study has some limitations. First, the actual inhalations were self-reported by the patients, which could have led to bias by overreporting actual use (and thus also an overestimation of unrecorded actuations), as patients might tend to provide socially desirable answers. However, as a 24-hour patient observation was not feasible, this was the best way to collect data on patients' actual drug intake within this setting. To prevent socially desirable answers, patients were instructed at the intake that this study was on verifying the registrations of the EIMD rather than their medication use or adherence, and during the phone calls, the students asked open questions. Additionally, patients were questioned about their actual inhalation mainly at the same and previous days, with a maximum of 5 days prior. Thus, the phone calls for data evaluation focused on the most recent moments of drug intake in order to reduce possible recall bias. In further analysis regarding the possible impact of recall bias, we did not observe any differences between measurements on day 5 and those on the earlier days, or between different age groups (data not shown). As earlier studies have shown that there is considerable variation in the accuracy of diaries to note medication intake (44), the use of a diary was not mandatory. As patients frequently reported technical issues as a possible explanation for both missing and extra registered inhalations, we do not expect much bias from this setting.



Second, all pharmacies were related to the master's education program of pharmacy from the University of Leiden. Data were collected in different pharmacies and by different students, to prevent bias from specific settings. However, such bias could not be fully excluded. Although the students were not yet registered health care providers, they were quite motivated and technically skillful. The students selected a convenience sample of patients, although it seemed difficult to find patients with the original inhalation medication that was fit for the EIMD; in some pharmacies, no patients could be selected at all. Third, the short inclusion time of this study, due to the internship period, could have led to selection of patients who were more willing to help the students with their task rather than being interested in their own medication performance or adherence. This was reflected in patients' individual comments: They regularly indicated that the program could be especially useful for other patients, but that it was of little value to them. Some patients reported that they did not need "help with the inhalation" or "an app for taking the medication." With a mean

medication adherence of >80%, this seems to be a group with relatively high adherence and could indicate selection bias of the more adherent patients, for which the device may be less useful. Further research is needed on how health care providers should preselect patients to whom they offer an EIMD on the basis of their experiences.

A strength of this study was the intensive follow-up from students, with more than 900 validated measurements. Although the number of included patients was limited, the number of drug intake comparisons was sufficient to detect omissions in the recorded actuations. However, the small population may have affected the representativeness of the results of the acceptability questionnaire. The statements in this questionnaire were formulated positively or negatively to reduce the risk of positively biased answers. This questionnaire was adapted to this specific EIMD and not validated beforehand. As a consequence, some patients might have experienced difficulties in comprehending the language used or the variety in both positively and negatively formulated questions.

### Implications for the Future

It is recommended that the discussed technical issues should be further elucidated and solved before using EIMD data as an objective adherence measurement, and medication overuse may also be of interest. In order to fully benefit from the EIMD and guarantee reliability and validity, an EIMD should be validated in a setting where the users interact with the system and can encounter technical or user issues. Furthermore, EIMDs and the accompanying self-management program should be evaluated on usability in daily practice. This study provided an example of how to do this. Validation of EIMDs in real-world settings is likely to improve usability in daily practice; the EIMD should be easy to use and measure all actuations correctly, even when the patient is not technically skilled. Future research should pay sufficient attention to different types of patient segments, as the EIMD needs to match with the patient profile (eg, adherence and asthma control), needs, and preferences.

## Conclusions

Comparison of EIMD data with patient-reported inhalations showed that EIMD registrations represented patient inhalations to an acceptable degree, with a PPV of 96%, but these registrations were likely to underreport actual drug intake by 11%. Technical improvements should address the Bluetooth connection and data synchronization. Additionally, patient characteristics contribute to the validity of EIMD measurements, and larger sample sizes are needed to explore their influence. For the acceptance of a self-management program with an EIMD, patients who benefit from self-monitoring and reminders should be targeted by tailoring the possibilities to the needs of the individual user.

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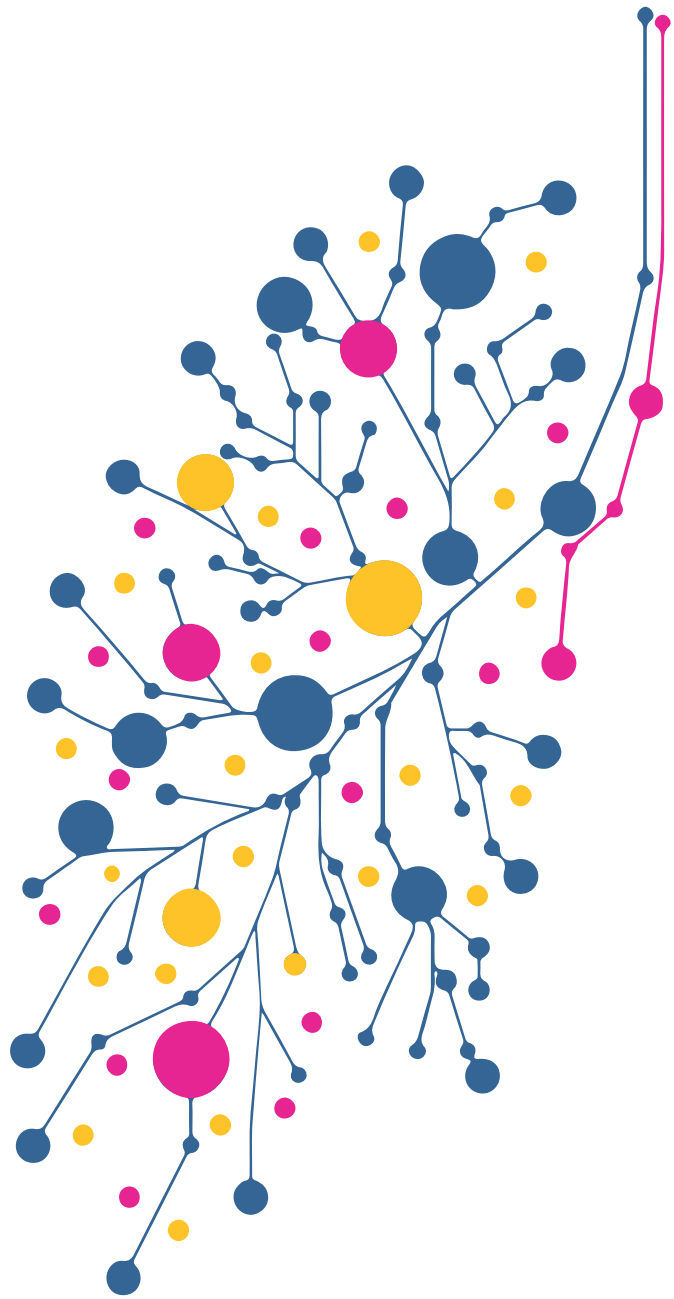
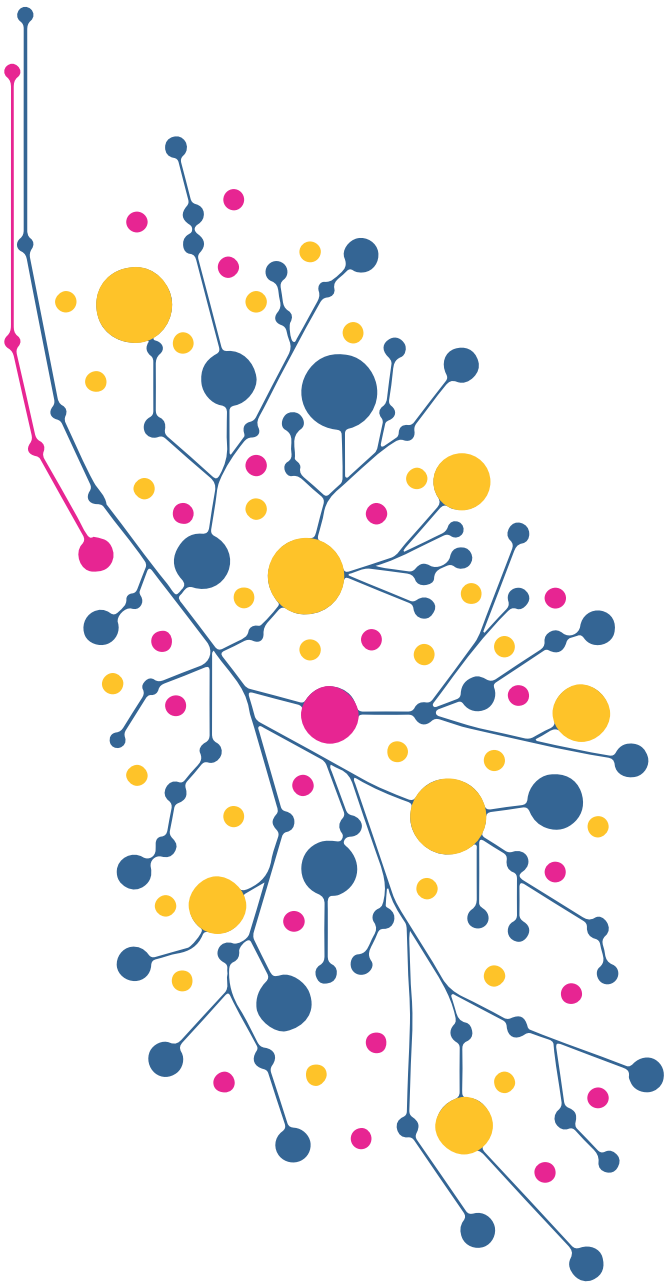


# Chapter 8

## General discussion



# General Discussion

Community pharmacists in the Netherlands are shifting their professional focus from medication distribution towards the provision of patient-centred pharmaceutical care (1-3). Pharmaceutical care in obstructive lung diseases like asthma and chronic obstructive pulmonary disease (COPD) is currently focused on the handling of computerized medication surveillance signals, giving inhalation instruction, and providing patients with information on disease and medication during dispensing visits, according to the prevailing guidelines (4). However, the adherence to those guidelines in current practice varies. Pharmacists are challenged to apply a more patient-tailored approach in daily practice and to adapt their protocol-based care to the needs and preferences of the individual patient. In this thesis, we investigated the status of current care in pharmacy practice and examined examples of pharmaceutical care activities for the future. This chapter first summarizes the main findings of the studies and then puts these results into a broader perspective.

# Main findings

## Current practice

We evaluated community pharmacists' adherence to professional guideline recommendations for pharmaceutical care to asthma patients with first dispensing and follow-up refill encounters in daily practice (chapter 2). Combining data on pharmacists' self-assessment, independent observations, and a questionnaire on pharmacists' views on the desirable (clinical) necessity of applying guideline recommendations to their patient population, revealed that the adherence to the guidelines varied across recommendations as well as pharmacists. The performance on information supply was generally highly consistent with recommendations, but the performance in exploring individual patient's needs was low.

This variation in guideline adherence was also observed in the use of non-selective (NS) β-blockers in patients with obstructive lung diseases (chapter 3). Although clinical guidelines recommended to avoid NS β-blockers in patients with asthma or COPD, a substantial number of prescribers was unaware of this co-morbidity or did not regard NS β-blockers contraindicated. The system regularly did not generate any signal, mainly because the lung medication did not appear as actual medication at the moment of initiation with the NS β-blocker. This occurred when medication was marked as 'temporary', and as a consequence, it disappeared automatically from the patient status when the calculated end date had passed. When the pharmacy system generated a medication surveillance signal, in most cases the NS β-blocker was dispensed and the patient was informed about the possibility of increased respiratory symptoms.

To encourage and boost pharmacists' participation in future pharmacy practice research, several factors were reported to be important (chapter 4). We found evidence that facilitating factors are: clear instructions by the researchers, possibilities for flexible time

management, simple patient inclusion, task delegation and no additional contacts with healthcare professionals due to the research.

### Future practice

Patient interviews shortly after the start with inhaled corticosteroids (ICS) maintenance therapy revealed various behavioural factors that might influence the achievement of individual treatment goals (chapter 5). Patients and pharmacists both felt positive about the interview and regarded this type of consultation as feasible in daily practice.

Pharmacist's monitoring of patients' disease control by means of the Control of Allergic Rhinitis and Asthma Test (CARAT) and timely tailored interventions in a general asthma population did not show effects on patient-reported disease control compared to usual care (chapter 6). The use of an electronic inhalation monitoring device (EIMD) was found to be potentially useful for helping patients with unintentional nonadherence to their medical treatment.

Besides this use in clinical practice, EIMD data could be used as an outcome measure for medication adherence, that may well be more objective than subjective querying of the patient (chapter 7). Results in laboratory settings might not apply to EIMD validity and reliability in the broad use by community-dwelling patients; patients' interaction with the device in real-world settings was shown to be critical for EIMD measurement of medication adherence. Comparison of EIMD data with patient-reported inhalations showed that EIMD registrations represented patient inhalations to an acceptable degree (positive predictive value of 96%), but these registrations were likely to underreport actual drug intake by 11%. For the acceptance of a self-management program with an EIMD in practice, patients who benefit from self-monitoring and reminders should be targeted and the possibilities of the device should be tailored to the needs of the individual user.

## Interpretation of the findings



The summarized results are put into a broader perspective, based on seven relevant topics: practice variation, medication surveillance, implementation, patient-centred care, targeting patients and tailoring interventions, self-management, and tools. The first three topics are related to current practice, the other topics to future practice.

### Practice variation

Evidence-based medicine (EBM) has been defined as "the integration of best research evidence with clinical expertise and patient values" (5). Guidelines have been developed according to these principles, reflecting the best available evidence to guide practice (6-9). The professional guidelines, developed by the Royal Dutch Association for the Advancement of Pharmacy (KNMP) generally describe the processes and preconditions within pharmacy practice to provide pharmaceutical care (e.g. multidisciplinary cooperation with other healthcare professionals, the dispensing process, patient monitoring and

counselling). The Dutch professional guideline for pharmaceutical care to patients with asthma, as well as the guideline for patients with COPD, is ahead of practice and contains ambitious recommendations, that the pharmacist should strive for. Pharmacists followed the guideline recommendations in daily practice on different levels (chapter 2). At first sight, this practice variation seems to be contradictory with the standardization of care, but deviation from the guideline may well be appropriate for individual patients, as a result of clinical expertise or specific patient values (6, 7). Pharmacists acknowledge that it should be possible to deviate or complement the recommendations in an individualized approach of patients, but for the large majority of recommendations for asthma care the performance observed in daily practice did not reach the score desired by the pharmacists themselves. Pharmacists are used to a protocol-driven way of providing pharmaceutical care and use checklists in daily practice regularly, also during medication surveillance. It is not always clear whether the reasons to deviate from guideline recommendations are justifiable, or if these decisions are merely based on other reasons (e.g. time pressure, incomplete patient files, pharmacists' preferences, untidiness, et cetera).

## Medication surveillance

In chapter 3, we described practice variation regarding the prescription and dispensing of NS β-blockers. The medication surveillance system facilitates the assessment of drug-disease and drug-drug interactions by providing guideline-based management options, but assessing the individual patient can be complex. In earlier studies the respiratory effect of β-blockers in people with asthma appeared to vary according to selectivity, dose and individual susceptibility (10, 11). Adding such individual patient risk factors to the medication surveillance system could be helpful in clinical decision making (11, 12). Also patient preferences should be part of this integrated risk assessment; a previous study has shown that there can be considerable variability in preferences among patients and pharmacists (e.g. in the perception of clinical risks and benefits, or practical implications) (13). For example, to explore the relevance of this drug-disease interaction, the pharmacy staff could prospectively monitor the occurrence of symptoms after the start with the NS β-blocker, in consultation with the patient. So, additional clinical and non-clinical information is needed to assess the relevance of the alert and to support the pharmacist in the risk management and evaluation.

## Implementation

Some pharmacists are hesitant to implement the professional guidelines, because these recommendations might be used too early, or inappropriately, for summative purposes (e.g. benchmarking or external evaluation), rather than for formative assessment (i.e. indicating the direction in which the pharmacist is expected to grow (14, 15)). In the past years, quality indicators have become more important in guideline implementation by monitoring and improving healthcare (14, 16). However, pharmacists experienced that these scores are not only used formatively, for internal audit and feedback, but also summatively: the insurance companies in the Netherlands use these scores to classify the care in pharmacies in different quality levels and a differentiated corresponding payment for their services. Thus, it is important that guideline developers state clearly how the guideline recommendations

should be applied. An earlier study has shown that this pay-for-performance approach may not only have a negative impact on a professional's job satisfaction, but does not contribute to a patient-focused approach either (17). Guidelines and quality indicators need to be applied critically, to avoid undesirable standardisation (18). Although the use of quality indicators can be useful to monitor the improvement of processes, there is a need to add other outcomes, that reflect and measure the individualized application of the guidelines (18, 19). For example, guidelines often address a single chronic disease and are not applicable for patients with multiple morbidities, as strict guideline adherence could lead to conflicting therapies (20-22).

Impact on clinical practice only can be reached by successful implementation of the guidelines into daily routines (8, 23). There are several success factors (facilitators) and barriers (e.g. agreement with the guideline or not, the capacity for organisational change) that might enable or prevent the healthcare professional to implement the recommendations in daily practice (24, 25). A previous study among primary care healthcare professionals showed that poor provider self-efficacy and lack of outcome expectancy were barriers for adherence to asthma management guidelines (26). We did not specifically study these barriers and facilitators regarding the implementation of professional guidelines in the Netherlands, but it is clear that they exist and play an important role. We also found a number of barriers and facilitators regarding participation in pharmacy practice research (chapter 4). Additionally, although pharmacists might be willing to participate in research, this does not naturally mean that they are performing all the requested tasks, in the right way. A clear example was described extensively in an earlier Dutch study: despite an initial response of 91 out of 305 pharmacies, there was a substantial number of pharmacies which had difficulties getting started or carrying out the intervention; just 50 of the 91 pharmacies completed the study as intended (27).

## Patient-centred care

The principles of EBM include the desirability and necessity of individualization of guideline recommendations and tailoring care to patients' needs and preferences, rather than justifying the delivery of uniform healthcare (6). The recently updated guidelines of the Global Initiative for Asthma (GINA) emphasises this patient-centred approach by recommending adjustment of the treatment up and down to individual patient needs and symptom-driven use of ICS in mild asthma (28, 29). So, pharmacists are challenged to not adhere to the recommendations too rigidly, but use these as a starting point for a patient-tailored approach and situational handling. Although the professional KNMP guidelines mention the importance of individualization of the recommendations, it is not clearly described when and how to tackle this challenge in daily practice.

Pharmacists should start with the recognition of and focus on patient's needs, preferences and perceptions, rather than just giving information or offering the same intervention to all patients. Apparently, the pharmacy staff is not yet used to responding to patients' individual needs (chapter 2). This is in line with earlier (both national and international) studies; pharmacy staff generally provided practical information, but rarely discussed patient's

preferences and perceptions about prescribed medication, or encouraged patients to ask their questions (30-35). Earlier studies have also shown that patients with chronic conditions have a need and a wish for counselling by the pharmacist (especially when they start with new medications), and the provision of appropriate, tailored information has the potential to improve patient knowledge and behaviour (e.g. medication adherence) (36-42). In chapter 5 of this thesis, patients revealed various perceptions and beliefs that might influence the achievement of their individual treatment goals. Pharmacists could not deduce from a person's basic characteristics whether additional care and which type of care were needed. So, pharmacists and their teams need to gather relevant information from and about their patients, when they have personal contact with them at strategic moments.

The actual exploration of patients' needs and preferences requires good communication skills and our results indicate that there are possibilities for improvement in this area (chapter 2). Earlier studies emphasised the importance of communication skills for pharmacists; good communication skills can encourage active patient participation (33, 43-46). Pharmaceutical encounters between the patient and the pharmacist are ideally based on reciprocal trust and shared decision-making, according to the Calgary-Cambridge guide (45, 47). This guide is currently widely used by physicians, and it is shown to be especially useful with regard to more complex skills, like encouraging patient participation and exploring patient beliefs and concerns (45, 48). The guide helps to give structure to the conversation and includes the following steps: initiating the session, gathering information, providing structure to the consultation, building relationship, explanation and planning, and closing the session (45). The Calgary-Cambridge guide can also be used as a tool for training pharmacists: as it differentiates the skills, the guide can help pharmacists to obtain insights in their own skills (45). However, not all patients might be able to participate in the process of shared decision-making. Patients need appropriate knowledge and perceived capacity to influence the decision-making encounter (49), and also organizational- and system-level factors seem to play a role (50). Future research should focus on the development of strategies for pharmacists to address these factors and profile their patients.

Information seeking and giving should be balanced during the encounters. Especially around the second dispensing of inhalation medication, pharmacists should actively seek information. As the pharmacist is occupied with many different activities and tasks (51), pharmaceutical encounters and other care activities in daily practice are also conducted by pharmacy assistants. So, communication skills are important for the whole professional pharmacy staff, not only during standard encounters in the pharmacy, but also in the demonstrations of inhaler technique skills (52).

## Targeting patients and tailoring interventions

For the majority of patients, standard care might be sufficient ('low need patients'). However, pharmacists are challenged to find the patients in need for additional pharmaceutical care ('high need patients'). There are a number of topics and areas within the treatment of obstructive lung diseases that require special attention and that could lead to a tailored intervention, for example with regards to self-management, disease control

(e.g. exacerbation frequency or limitations in daily life), medication adherence, inhalation technique, and smoking cessation. In this thesis, we have explored some examples of possible tailored interventions in chapter 6. Depending on the patient's CARAT score, the pharmacist for example inquired about hay fever symptoms, recommended the use of antihistamines or nasal corticosteroids, discussed the importance of medication adherence and referred to the general practitioner for the examination of a possible exacerbation. In a systematic review, tailored interventions during care transitions (for example by assessing patients' knowledge about the prescribed medication) were found to be more effective than applying a general approach, and the effectiveness of pharmacist interventions might be increased by collaboration with other healthcare professionals (53).

It is clear that not all interventions are suitable for all patients. For example, education and help with smoking cessation is essential in both COPD and asthma disease management (54, 55), and trained community pharmacists might be effective in delivering smoking cessation interventions (56-58). However, education on smoking cessation is only relevant if the patient is a current smoker, and wants to be supported in quitting. There might be additional information needed when there are comorbidities or when a patient uses CYP1A2 metabolized medication (59).

In current practice, the pharmacy staff plays an important role in training the patient with the inhaler device technique; patients need to achieve correct inhaler technique at the start of the therapy, but also maintain appropriate use of the inhaler over time (60-64). Earlier studies have shown that the quality of the inhaler technique tends to decline over time, when no further education is provided (63-65). So national and international guidelines recommend checking the inhalation technique preferably at every opportunity, but at least with the second dispensing and annually thereafter (66-68). However, for some patients it might be useful to check this more often, as the inhaler technique might already decrease in just a few months (65).

This thesis shows that there are possibilities for the pharmacist to identify patients whose lung disease may not be well controlled, during dispensing moments as well as apart from these moments. Pharmacists should realize that they are in an excellent position to support patients after the start with new chronic medication, and also to detect patients whose disease gets uncontrolled and offer an intervention in time. Patterns of medication dispensings could indicate that a patient experiences problems (e.g. overuse of reliever medication, underuse or overuse of maintenance medication, or short courses of oral corticosteroids). Although this information is useful, the pharmacy staff should ask for the clinical status or patients' clinical goals. At present, pharmacists usually have contact with their patients during dispensing visits only. However, some patients may develop less controlled asthma in the meantime, and poorly adherent patients may not show up for subsequent dispensing at all. Separating pharmaceutical care from the medication delivery process can provide additional timely insights in patients' goals, needs and wants, as described in chapter 5. An earlier study showed that some patients newly having started with chronic medication may quickly become non-adherent and that many of them

experienced problems with medication and needed additional information (69). So this period is important for the start and subsequent adherence; patients are more focused on the new therapy and their health, and outreach in this period has the potential to positively impact long-term care (30, 31, 39, 70, 71).

There are several patient characteristics that play an important role in their disease management. For example, an earlier study showed that approximately 50% of the patients in the Netherlands have limited health literacy skills; these patients experienced difficulties in understanding medication label instructions (72), which might possibly result in drug therapy related problems (73, 74). It is important to identify these individuals, for example, by using a medication-specific approach that provides insights in the level of skills that are required for adequate medication use (75, 76).

## Self-management

Although obstructive lung diseases are mostly manageable with medication and non-pharmacological treatment strategies, these conditions are not curable (67, 68). So, as they live with these conditions for many years, patients should proactively manage their disease by themselves (77). However, many patients only attend to their healthcare providers when there already are problems (78). So ideally, patients should cooperate with their healthcare professionals in monitoring symptoms and actively manage their disease control. Collaboration and effective communication between pharmacists and general practitioners (GPs) could potentially increase drug therapy optimization and enhance patient safety (79, 80). Pharmacists should encourage patients in improving their self-management skills, as this can lead to improved awareness and competence in disease management (81, 82). However, self-management may not be feasible for all patients and this support should also be individualised. Earlier studies regarding self-monitoring and self-management in patients with oral anticoagulation therapy indicated that a large number of patients might not be able to self-management, and revealed that patients encountered a number of barriers (83, 84). For example, patients' attitude, physical limitations, the inability to use a monitor device properly, and the inability to participate and successfully complete a training (83, 84). Studies on self-management in asthma patients explored also a number of factors that influenced the uptake or outcomes of self-management strategies, for example health beliefs, partnership between the patient and healthcare provider, and co-morbidities (85). Additionally, studies in adolescents showed important psychosocial factors, like negativity towards healthcare providers and the medication regimen, peer influences, and denial (86, 87).

## Tools

We described two possible tools for proactive patient monitoring, that can be used in addition to dispensing data: an EIMD and the CARAT questionnaire (chapters 6 and 7). These tools can be used individually, but also in combination. An EIMD can provide both the patient and the pharmacist with detailed information on patient adherence to treatment (88-91). These data offer additional insights into daily medication use; patients may collect their medication, but this does not naturally mean that they are going to use it as prescribed.

Considering the reminder and feedback function, an EIMD might be effective to support non-intentional non-adherence. Pharmacists should be aware of the possibility that patients' refusal of using an EIMD might indicate the existence of intentional non-adherence.

Besides, an EIMD can be useful in daily practice to enhance patients' self-management skills and patient-pharmacist interaction (92-94). Recognizing deterioration in disease control, or clinical symptoms, is important, because a timely intervention could potentially minimize the risk for the development of a severe exacerbation (77). Patients might not always know that they need additional care, because they could consider their situation as normal, or have accepted their symptoms or limitations in daily life. In the SMARAGD study (chapter 6), the use of the CARAT questionnaire by an application on the mobile phone was shown to be helpful in daily practice to identify patients that were in need of an intervention. The questionnaire enabled patients to monitor themselves and gave the pharmacist the opportunity to offer tailored interventions. Patients and pharmacists felt positive about the questionnaire as self-management tool, which could be actively offered to patients, for example during the annual check of the inhalation technique (which could also identify patients in need for an intervention in this area).

The described tools for pharmaceutical care activities are employable for multiple purposes; they can not only be used as a diagnostic tool (to identify high need patients) but also in monitoring the effects of a tailored intervention. However, all intervention components should be critically reviewed on usability and patients should be given options for individualization, in consultation with their healthcare provider. For example, the studied EIMD included several functionalities (e.g. motivational messaging, reminder function, and audio-visual behavioural feedback) that were not equally appreciated by all patients (chapter 7). This is in line with earlier studies, that described electronic health apps that did not perform as expected in clinical practice, because the application turned out to be unacceptable or did not fit the users' needs (95-98). So, there should be possibilities for both patients and pharmacists to emphasize some components of the intervention, switch off unnecessary functionalities or adapt the content to individual patient needs, preferences and characteristics (e.g. disease control or health literacy skills).



## Methodological considerations

Most of our research was performed in small, convenience samples of pharmacies. This pragmatic approach might have led to selection bias: the pharmacies and pharmacists in the studies might not represent the general population, so our results cannot be generalized for all community pharmacies in the Netherlands. Although we compared the pharmacy characteristics and concluded that those generally did not differ from the national data (99), there could be practice variation, which influenced the representativeness.

Two of our studies were performed by students (chapters 2 and 7), and one by pharmacists during their national postgraduate specialization programme to become community

pharmacists (chapter 3). Due to the strict and defined period by the educational programmes, they had to select convenience patient samples. Besides, in chapters 6 and 7 we selected convenience sample of patients who were interested in eHealth. These results might not represent the whole population with obstructive lung diseases, but we needed specifically patients who were willing to use the EIMD. Besides, it remained unclear whether the participating patients were the population that benefit most from pharmaceutical care or the intervention.

Patient comorbidities and other characteristics could have contributed to the outcomes of the study. For example, adolescents and children were excluded from the studies, while asthma is a common and relevant condition in these age groups (100).

Parts of our research contained self-reported data, both from patients (chapters 6 and 7) and pharmacists (chapters 2 and 4), which could have led to socially desirable answers. In three of our studies, we combined qualitative and quantitative analyses (chapters 3, 6 and 7). This mixed-methods approach is helpful for the purposes of breadth and depth of understanding and corroboration (101).

Some of the studies (chapters 2 and 6) focused on patients diagnosed with asthma, while in other studies (chapters 3, 5 and 7) all patients were included that used ICS maintenance therapy. It is difficult to recognize the underlying lung disease based on the medication alone; this requires the exchange of diagnostic information between lung specialists, GPs and pharmacists. However, the specific diagnosis was not relevant for the interpretation of the findings. Although the clinical importance for the use of ICS is different for asthma compared to other obstructive diseases, ICS are currently prescribed as maintenance therapy for regular use in all conditions.

# Implications for practice

## Guideline individualization

To individualize guideline recommendations, pharmacists need adequate tools to target and differentiate between patients. Besides, it is recommended to clarify and describe the quality of evidence for the individual recommendations of the professional guidelines, e.g., by using the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach. GRADE provides guidance for assessing the quality of evidence and patient outcomes, and indicates the strength of a recommendation in order to help healthcare providers in their (shared) decision-making process (7, 102). Moreover, the quality of healthcare should not only be assessed as compliance with guidelines without addressing (clinical) patient outcomes.

## Proactive monitoring

This thesis showed that pharmaceutical care is not necessarily connected to the medication delivery process and that pharmacists have other options for monitoring their patients

proactively. It is recommended that the medication surveillance systems evolve further, so that individual risk factors and patient preferences become part of the integrated risk assessment. Currently, several computerized medication monitoring systems are available to trace patients who do not return for their refill dispensing, patients with ICS and short oral corticosteroid courses or antifungal medication, patients who did not receive a new spacer in the last year, patients with overuse of SABA, et cetera. In addition to these signals, the pharmacy staff has the opportunity to detect drug therapy related problems or patient's needs and wishes. Cooperation with other healthcare professionals may also reveal important information. For example, home care organisations could be encouraged to use the 'Red Flagg Instrument', which has been developed to detect drug therapy related problems in home care (103). Pharmacists should make agreements with other healthcare professionals, especially in primary care settings, about their cooperation in the identification of high need patients, referral to each other, and the division of tasks when offering the necessary interventions. It might be more appropriate that some (parts of) interventions are performed by other healthcare providers (e.g. general practitioner, pulmonary nurse, or physiotherapist).

An additional moment of contact 2-3 weeks after the start with ICS, before the moment of a second dispensing of inhaled medication, is pre-eminently suitable for the pharmacy staff to ask for patients' first experiences, needs and preferences. Especially with inhaled medication, the recognition of problems could be delayed, as refills with inhalers containing a large number of doses (e.g. 200 doses in some pressurized Metered Dose Inhalers) could take some time. In the meantime, patients may experience problems, or poorly adherent patients may not show up for subsequent dispensing at all. Implementation of these care activities in daily practice should be encouraged by reimbursements for those consultations or related interventions. Dutch healthcare insurance companies currently provide a reimbursement only for the first dispensing consultations.

## Pharmacists' needs and wants

For healthcare providers, a 'one size fits all' approach is also not appropriate; not all pharmacists are equally skilled, so they may need education or training in different areas. For example, healthcare professionals could lack tools or sufficient skills to support their patients in self-management (77). Besides, to perform integrated risk assessments in addition to the medication surveillance systems, they need clinical reasoning competences (104). Besides, to ask and interpret someone's needs, and to develop towards the role of a patient's coach, communication skills of the pharmacist are crucial. Pharmacists need to be aware of and increase the specific skills required to conduct patient-centred consultation (45). The Calgary-Cambridge guide could help the pharmacy team to improve and check their consultation skills. A small-scale exploration of the barriers and facilitators for the implementation of this guide in daily practice showed positive results: pharmacists and their team regarded it feasible to use, and they emphasized the need of education (105).

Within the current community pharmacist education programmes (master and national postgraduate specialization programme), there is increasing attention for these

communication skills. However, pharmacists were traditionally trained with a product-centred focus in the past, and there might be a group of practising pharmacists that is not yet sufficiently skilled in applying a patient-centred approach and clinical reasoning. They have to decide individually whether they are open for training in these areas, or that other options have to be considered (e.g. differentiation and specialisation in specific tasks).

## Implications for research

The research in this thesis provide a number of suggestions for further pharmacy practice research. Future research should pay attention to the needs and preferences of specific patient groups, like children and adolescents with asthma, patients with comorbidities, patients with medication overuse, low (health) literacy skills, etc. It is still unknown which patients benefit most from which service, and why. In addition, research is required to examine the ability of pharmacists to recognize patients' willingness and skills for self-management, and the best way to address these. The Self-Management Screening questionnaire (SeMaS) might be a useful tool for pharmacy practice; this questionnaire assesses patients' potential barriers for self-management that need to be discussed in an individual dialogue with their healthcare provider (106, 107). There are also different factors that influence the behaviour of pharmacists and pharmacy assistants, for example, in their application of and adherence to guidelines, the Calgary-Cambridge guide and their ability to individualize the recommendations (e.g. skills for communication and clinical reasoning). These barriers and facilitators need to be explored in pharmacy practice research.

Further research should focus on the potential benefit and cost-effectiveness of pharmacists' proactive monitoring and the effects of timely tailored interventions on clinical outcomes (e.g. disease control) and medication adherence. Although medication adherence and disease control are positively correlated (108), in studies and daily practice we tend to focus on medication adherence as an outcome measure, rather than looking at (changes in) the patients' clinical status. Some of the followed patients in the SMARAGD study remained stable at the maximum CARAT score (which means maximal disease control), while the medication adherence could be classified as 'low' (e.g. 50-70%). These results emphasize the necessity of adding clinical outcomes and adjust the treatment (up or down) for individual patient needs, which is also reflected in the updated GINA guidelines. The changes in these guidelines represent a major reorientation in the treatment of a large group of asthma patients, and the implications of these changes have to be studied (28).

## General conclusions

Pharmacists need to grow into a patient-centred approach in their care activities. They should focus more on seeking relevant patient information and exploring patients' individual needs and preferences, rather than providing practical information only. Information seeking and giving should be balanced during the encounters with the patient. Pharmacists are,

in collaboration with other primary care healthcare professionals, in an excellent position to identify high need patients (e.g. impaired disease control, low adherence rates) and to offer tailored interventions. Pharmacists should pay attention to the registration of their care activities, to demonstrate whether deviation from guideline recommendations is justifiable and whether it could be regarded as well-considered tailored pharmaceutical care. Future research should focus on the potential benefit and cost-effectiveness for individualized, tailored pharmacists' interventions, like early (telephone) consultation and the use of an EIMD, and the effects on clinical outcomes.

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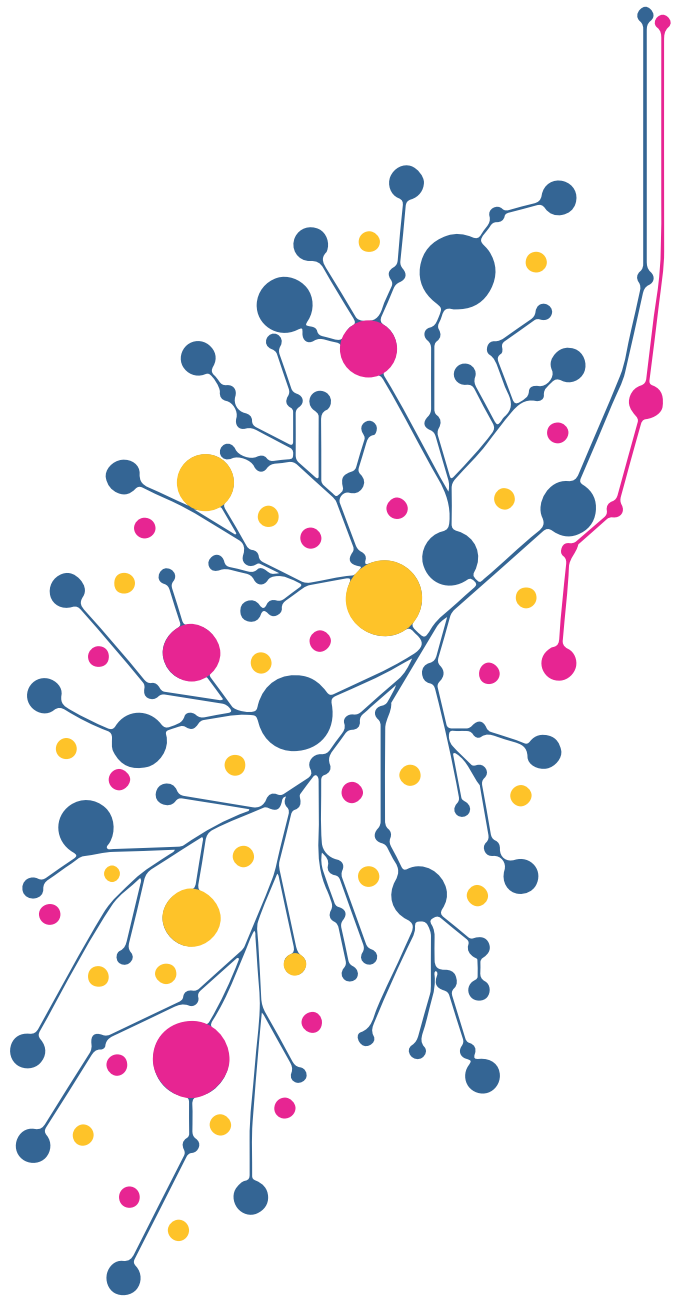
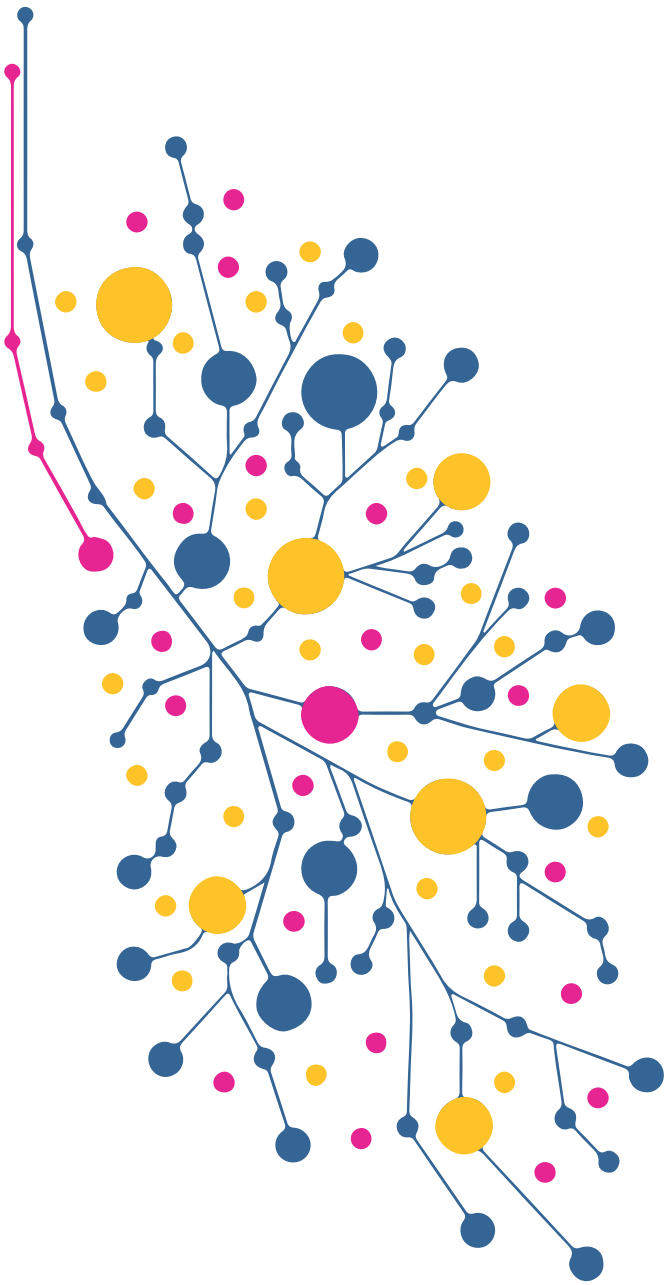


# Appendices




Summary
Samenvatting
Dankwoord
About the author
List of co-authors
List of publications
Data management
PhD Portfolio

# Summary

The profession of community pharmacists has extended the traditional role of medication dispensing towards the provision of patient-centred pharmaceutical care. At present, the pharmacist's role in the treatment of obstructive lung diseases mainly includes providing patients with information on disease and medication use during dispensing visits, handling computerized medication surveillance signals and giving inhalation instruction. In this thesis we focused on improving the insight into the current status (chapter 2-4) and future possibilities (chapter 5-7) of pharmaceutical care in patients with obstructive lung diseases.

As there is a need for standardisation of care that reflects the best available evidence to guide practice, guidelines have been developed according to the principles of evidence-based medicine. Pharmaceutical care guidelines aim to provide recommendations for pharmaceutical care, reduce unwanted pharmacy practice variation and ultimately improve the quality of healthcare. **Chapter 2** presents the evaluation of pharmacists' adherence to recommendations for the provision of care to asthma patients with first dispensing and refill encounters in daily practice. Combining data on pharmacists' self-assessment, independent observations, and a questionnaire on pharmacists' views on the desirable (clinical) necessity of applying guideline recommendations to their patient population revealed that the adherence to the guidelines varied across recommendations as well as pharmacists. The performance on information supply was generally high, but the performance in exploring individual patient's needs was low. The pharmacy staff rarely asked for patients' perceptions, expectations, wishes and concerns.

Although clinical guidelines recommended to avoid non-selective (NS) β-blockers in patients with obstructive lung diseases, on average, 10 patients per community pharmacy receive NS β-blockers monthly. **Chapter 3** describes reasons of prescribers and pharmacists to treat asthma and chronic obstructive pulmonary disease (COPD) patients with NS β-blockers. 153 NS β-blocker prescribers were questioned; a substantial number of prescribers was unaware of the co-morbidity or did not consider the drug-disease interaction to be relevant. For 299 patients, medication surveillance signals and pharmacists' actions at the moment of first dispensing were retrieved. The surveillance system did not always signalize these drug-disease interaction appropriately; the system regularly did not generate any signal. When the pharmacy system generated a medication surveillance signal, in most cases the NS β-blocker was dispensed and the patient received information from the pharmacist about the possibility of increased respiratory symptoms.

Practice-based research in community pharmacies is essential for the advancement of the academic pharmacists' profession and for further development of pharmaceutical care. Nevertheless, conducting pharmacy practice research can be challenging in daily practice. In **chapter 4** we explored the attitudes and motivation of community pharmacists in the Netherlands to participate in pharmacy practice research. 252 pharmacists completed the online questionnaire. Time investment and a clear added value for the profession, patient or pharmacy were the most important factors in the decision to participate in the

research. Feasible study designs may encourage pharmacists' participation in pharmacy practice research: pharmacists were more likely to participate when tasks could be delegated and spread over time or when they could invite patients for participation by email. Researchers are recommended to offer clear instructions, provide possibilities for a flexible time management and task delegation, avoid collection of obviate data and unnecessary complicated patient selection, and only ask for additional contacts with other healthcare professionals when needed.

For future practice, pharmacists are challenged to apply a more patient-tailored approach in daily practice and adapt the pharmaceutical care to the needs and preferences of the individual patient. Shortly after the start with inhaled corticosteroids (ICS) maintenance therapy, patients with an obstructive lung disease may be in need of additional pharmaceutical care. In **chapter 5** we present a qualitative study which aimed to obtain insight into personal goals and perceptions regarding medication use in ICS starters. 5 pharmacists conducted semi-structured telephone interviews with 23 adult patients, 2-3 weeks after their start with ICS. The patient interviews were audiotaped and transcribed verbatim. The Theoretical Domain Framework (TDF) was used for data analysis and coding. After the interviews, both patients and pharmacists were questioned about their experiences with these interviews and their opinions on the utility of this type of consultation for regular daily practice. The interviews revealed various perceptions and beliefs that might influence the achievement of individual treatment goals. The majority of patients defined clear personal goals, which mainly addressed disease or symptom control. Patients described different perceptions on the need to develop a personalized routine for regular medication use. Some patients were convinced of beneficial effects of the medication, while others doubted this benefit. Some interviewees showed a lack of knowledge regarding the clinical indication or therapy duration, and others specifically mentioned concerns or anxiety about side effects. The patients appreciated the opportunity to ask questions and share their perspectives and needs with their pharmacist; they regarded an additional telephone consult with the pharmacist to be useful, even when they personally did not have problems or questions at that moment. All pharmacists felt that the telephone consultation had added value for patients, but also to themselves (e.g. the opportunity to obtain early insights in patients' thoughts and motivation regarding their medication use).

Timely interventions, targeted at patients with suboptimal disease control may be useful in preventing exacerbations and deteriorating disease control between dispensing visits. **Chapter 6** describes a pilot trial to assess the effectiveness of tailored pharmacists' interventions on patients' asthma control by prospective monitoring with patient-reported disease control scores, compared with a control group receiving usual care. 39 asthma patients using ICS were included in the intervention group (IG) and 41 in the control group (CG). IG patients completed the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire every 2 weeks and received tailored counselling on disease management, ICS adherence, and inhalation technique when scores were suboptimal, deteriorating, or absent. Additionally, for the users of the Turbuhaler, an electronic monitoring device (EIMD) was available. This EIMD, which measures inhalation actuations, reminds patients

with respiratory diseases to take their medication and provides detailed data on patient adherence to treatment to both patient and health care providers. After the follow-up period of 6 months, pharmacist's monitoring of patients' disease control and timely tailored interventions did not show any effects on patient-reported disease control, compared to usual care. However, the use of an EIMD showed improved ICS refill adherence; an EIMD might be potentially useful for helping patients with unintentional non-adherence to medical treatment.

Besides use in clinical practice, EIMD data could be used as an objective outcome measure for medication adherence, that is more objective than subjective querying of the patient. However, it is important that EIMD measurements are accurate and valid: results in laboratory settings might not apply to EIMD validity and reliability in the broad use by community-dwelling patients. **Chapter 7** describes the validity assessment of an EIMD, and the patient-reported usability and acceptability. We conducted a prospective observational study on agreement between EIMD measurements and patient-reported inhalations in 21 community pharmacies. 32 patients were included and 932 medication doses were validated. We found an acceptable positive predictive value; 96.0% of the registered doses represented patient-reported drug intake. However, we found a high number of false negative registrations; 11.1% of patient-reported inhalations were not recorded by the EMD.

Overall, patients considered the EIMD to be acceptable and easy to use, but many hesitated to continue its use. Reminders and motivational messages were not appreciated by all users, and more user-tailored features in the app were desired. Patients' interaction with the device in real-world settings was shown to be critical for EIMD measurement of medication adherence.

In **chapter 8**, the findings of the studies are discussed and considered into a broader perspective. For the majority of patients standard care might be sufficient, but pharmacists have opportunities to identify patients in need for additional pharmaceutical care. There is a need for pharmacists to focus on seeking for relevant patient information and exploring patients' individual needs and preferences, rather than only providing practical information. Also regarding the medication surveillance system, it is important to add individual risk factors and patient preferences, so that these factors become part of the integrated risk assessment. Pharmacists are challenged to apply professional guideline recommendations not too rigidly, but to use these as a starting point for a patient-tailored approach and situational handling. Although the use of quality indicators can be useful to monitor the improvement of processes, there is a need to add other outcomes, that reflect and measure this individualized application of the guidelines. Pharmacists are, in collaboration with other primary care professionals, in an excellent position to identify the high need patients (e.g. impaired disease control, low adherence rates) and to offer tailored interventions. They have opportunities to support patients in the important period shortly after the start with new chronic medication, to encourage patients in improving their self-management skills and also to detect patients whose disease gets uncontrolled over time. We described two possible tools for proactive patient monitoring, that can be used for timely interventions in

addition to dispensing data: regular use of the CARAT-questionnaire and an EIMD. These tools can be used as a diagnostic tool to identify high need patients, but also in monitoring the effects of a tailored intervention. However, all components of any intervention should be critically reviewed on usability and patients should be given options for individualization, in consultation with their healthcare provider.

There is a need to explore the barriers and facilitators of pharmacists and pharmacy assistants that influence their behaviour regarding the application of - and adherence to professional guidelines, and their ability to individualize the recommendations (e.g. skills for communication and clinical reasoning). Future research should focus on the potential benefit and cost-effectiveness for individualized, tailored pharmacists' interventions, and the effects on clinical outcomes.

# Samenvatting

Het beroep van openbaar apothekers maakt een ontwikkeling door; de traditionele rol van het verstrekken van medicatie verschuift naar het leveren van patiëntgerichte farmaceutische zorg. Op dit moment spelen apothekers bij de begeleiding van patiënten met obstructieve longaandoeningen met name een rol in het verstrekken van informatie aan patiënten. Zij geven, vooral tijdens de aflevermomenten, informatie over het gebruik van de medicatie en de aandoening en zij handelen de geautomatiseerde bewakingssignalen af. In het eerste deel van dit proefschrift hebben we ons gericht op het verkrijgen van inzichten in de huidige praktijk (hoofdstuk 2-4). In het tweede deel hebben wij toekomstige mogelijkheden voor farmaceutische zorg bij patiënten met obstructieve longziekten verkend (hoofdstuk 5-7).

Richtlijnen zijn een leidraad voor de zorg in de praktijk. Zij worden ontwikkeld op basis van het best beschikbare wetenschappelijke bewijs, volgens de principes van 'evidence-based medicine'. Richtlijnen voor farmaceutische zorg zijn bedoeld om richting te geven aan de inhoud van de zorg door de apotheker. De apothekersorganisatie KNMP ontwikkelt richtlijnen voor de openbare farmacie. Zij dienen ongewenste variatie in de apotheekpraktijk te verminderen en uiteindelijk de kwaliteit van de gezondheidszorg voor de patiënt te verbeteren. **Hoofdstuk 2** presenteert de evaluatie van de opvolging van de aanbevelingen uit de KNMP-richtlijn Astma voor zorg bij de eerste-, tweede- en vervolguitgiften door apothekers in de dagelijkse praktijk. Hiervoor werden drie evaluaties gecombineerd: eerst werden apothekers gevraagd om zelf de implementatiegraad van een aanbeveling in te schatten. Vervolgens observeerden farmaciestudenten als onafhankelijke personen uitgiftegesprekken en scoorden zij het opvolgen van de richtlijnadviezen. Een landelijke vragenlijst leverde daarnaast inzichten over de opvattingen van apothekers over de wenselijke (klinische) noodzaak om aanbevelingen voor richtlijnen toe te passen op hun patiëntenpopulatie. Dit onderzoek liet zien dat de implementatie verschilde voor de afzonderlijke aanbevelingen, en ook waren deze verschillend geïmplementeerd door apothekers. Bij de zelfinschatting en observaties werd in het algemeen hoog gescoord op het gebied van informatievoorziening, daarentegen werd er laag gescoord op het verkennen van de behoeften van individuele patiënten. De apothekers en -assistenten vroegen zelden naar de meningen, verwachtingen, wensen en zorgen van de patiënten.

Hoewel de klinische richtlijnen aangeven dat niet-selectieve (NS) β-blokkers zijn gecontra-indiceerd bij patiënten met obstructieve longaandoeningen, gebruiken volgens apotheek-aflevergegevens van de Stichting Farmaceutische Kengetallen maandelijks gemiddeld 10 patiënten per openbare apotheek NS β-blokkers. **Hoofdstuk 3** beschrijft de redenen van voorschrijvers en apothekers om deze patiënten met NS-β-blokkers te behandelen. Hiervoor hebben apothekers in totaal 153 voorschrijvers van NS β-blokkers ondervraagd. Een aanzienlijk aantal voorschrijvers was zich niet bewust van de co morbiditeit of vond de contra-indicatie niet relevant. Voor 299 patiënten werden de medicatiebewakingssignalen en apothekersacties op het moment van de eerste

aflevering teruggezocht. Het medicatiebewakingssysteem signaleerde de contra-indicatie niet altijd correct. Regelmatig werd er geen bewakingssignaal gegenereerd. Wanneer er wel een signaal in beeld kwam, werd in de meeste gevallen toch de NS β-blokker afgeleverd en wees de apotheker de patiënt op de mogelijkheid van verergering van de respiratoire klachten.

Praktijkonderzoek in de openbare apotheek is essentieel voor het wetenschappelijk beroep van academisch opgeleide apothekers en voor de verdere ontwikkeling van farmaceutische zorg. Desalniettemin kan het uitvoeren van farmaceutisch praktijkonderzoek een uitdaging zijn in de dagelijkse praktijk. In **hoofdstuk 4** hebben we de houding en motivatie van openbare apothekers in Nederland betreffende de deelname aan farmaceutisch praktijkonderzoek in kaart gebracht. 252 apothekers vulden een online vragenlijst in over hun opvattingen over praktijkonderzoek en de voorwaarden waaronder zij bereid zijn hieraan mee te doen. Beperkte tijdsinvestering en een duidelijke meerwaarde voor het beroep, de patiënt of de apotheek waren de belangrijkste invloedfactoren bij de beslissing voor deelname aan een onderzoek. Een haalbare onderzoeksopzet leek apothekers aan te moedigen om aan praktijkonderzoek mee te doen: apothekers waren eerder geneigd deel te nemen als taken gedelegeerd en verspreid over de tijd uitgevoerd konden worden, of wanneer ze patiënten konden werven via e-mail in plaats van persoonlijk. Op basis van deze resultaten dienen onderzoekers bij het opzetten van praktijkonderzoek te zorgen voor duidelijke instructies, mogelijkheden voor een flexibele tijdsindeling en taakdelegatie. Daarnaast moeten zij de verzameling van overbodige gegevens en onnodige gecompliceerde selectie van patiënten vermijden, en alleen vragen om samenwerking met andere zorgverleners wanneer dat voor het onderzoek echt noodzakelijk is.

Gepersonaliseerde zorg daagt apothekers uit om meer zorg op maat te bieden en de farmaceutische zorg aan te passen aan de behoeften en voorkeuren van de individuele patiënt. Kort na de start met een onderhoudsbehandeling met inhalatiecorticosteroïden (ICS) hebben patiënten met een obstructieve longziekte mogelijk behoefte aan extra farmaceutische zorg. In **hoofdstuk 5** presenteren we een kwalitatief onderzoek, dat is opgezet om inzicht te krijgen in persoonlijke doelen en percepties van patiënten die net startten met ICS. Vijf apothekers hebben semi-gestructureerde telefonische interviews afgenomen bij 23 volwassen patiënten, 2-3 weken na de start met ICS. De interviews met de patiënten werden opgenomen en woordelijk getranscribeerd. We gebruikten een model naar menselijk gedrag uit de psychologie, het Theoretical Domain Framework (TDF), voor data-analyse en codering. Uit de interviews met de patiënten kwamen verschillende percepties en overtuigingen naar voren die van invloed kunnen zijn op het bereiken van individuele behandeldoelen. De meerderheid van de patiënten omschreef duidelijke persoonlijke doelen, die voornamelijk betrekking hadden op het verminderen van de klachten en verbetering van de aandoening. Patiënten hadden verschillende ideeën over de noodzaak om een gepersonaliseerde routine te ontwikkelen om de medicatie regelmatig in te nemen. Sommige patiënten waren overtuigd van de gunstige effecten van de medicatie, terwijl anderen nog aan dit voordeel twijfelden. Sommige

geïnterviewden toonden een gebrek aan kennis met betrekking tot de klinische indicatie of de duur van de therapie. Anderen benoemden specifiek hun zorgen of bezorgdheid over bijwerkingen. Na de interviews werden zowel patiënten als apothekers gevraagd naar hun ervaringen met aanvullende adviesgesprekken en naar hun mening over het nut van dit soort consulten voor de dagelijkse praktijk. De patiënten waardeerden de mogelijkheid om vragen te stellen en hun mening en behoeften te delen met hun apotheker. Ze gaven aan een telefonisch consult met de apotheker nuttig te vinden, ook als ze op dat moment zelf geen problemen of vragen hadden. Alle apothekers vonden dat het telefonische consult meerwaarde had voor patiënten en voor hun zorg belangrijke inzichten opleverde. Het gaf hen bijvoorbeeld de mogelijkheid om op tijd inzicht te krijgen in de perceptie en motivatie van patiënten met betrekking tot hun medicatiegebruik.

Inhalatiemedicatie wordt meestal voor een langere periode meegegeven aan de patiënt, gewoonlijk voor 3 maanden. Tussen de aflevermomenten kan de ziektecontrole verslechteren. Het tijdig aanbieden van een interventie op maat kan voor deze patiënten nuttig zijn om een exacerbatie of ziekenhuisopname te voorkómen. **Hoofdstuk 6** beschrijft een pilot onderzoek naar de effectiviteit van interventies door apothekers op de astmacontrole. 39 astmapatiënten die dagelijks ICS gebruikten, werden geïncludeerd in de interventiegroep (IG). 41 patiënten in de controlegroep (CG) kregen gebruikelijke zorg. De IG-patiënten vulden elke 2 weken de 'Control of Allergic Rhinitis and Asthma' (CARAT) vragenlijst in. Indien de scores niet optimaal, verslechterd of afwezig waren, ontvingen zij advies op maat over ziektemanagement, therapietrouw en inhalatietechniek. Daarnaast was voor de gebruikers van de Turbuhaler een apparaat voor elektronische monitoring (EIMD) beschikbaar. Deze EIMD mat de activatie van de inhalator en herinnerde patiënten aan inname van hun medicatie. De EIMD-registraties boden gedetailleerde informatie aan zowel patiënten als zorgverleners over de therapietrouw met de inhalator. Na een periode van 6 maanden bleken gerichte interventies door de apotheker bij een slechte score op de CARAT vragenlijst geen effect te hebben op de ziektecontrole, vergeleken met de gebruikelijke zorg. Het gebruik van een EIMD liet echter wel een verbetering zien in de therapietrouw van ICS vergeleken met patiënten die geen EIMD gebruikten. Een EIMD kan mogelijk nuttig zijn ter ondersteuning van patiënten met niet-intentionele therapie-ontrouw.

Naast toepassing in de klinische praktijk, kunnen metingen van een EIMD worden gebruikt om therapietrouw valide te meten; immers zijn EIMD metingen objectiever dan subjectieve inschattingen van de patiënt. Hiervoor is het echter belangrijk dat EIMD-metingen nauwkeurig en correct zijn, ook in de dagelijkse praktijk. **Hoofdstuk 7** beschrijft de validiteitsbeoordeling van een EIMD en de ervaring van patiënten met betrekking tot de bruikbaarheid en acceptatie. We hebben een prospectieve observationele studie uitgevoerd naar de mate van overeenstemming tussen EIMD-metingen en door de patiënt gerapporteerde inhalaties in 21 openbare apotheken. 32 patiënten werden geïncludeerd in deze studie en 932 medicatiedoses werden gevalideerd. We vonden een acceptabele positief voorspellende waarde van 96%: dit percentage van de geregistreerde doses kwam overeen met de door de patiënt gerapporteerde inname van de medicatie. Er bleek

echter een groot aantal inhalaties te missen in de registraties ('fout negatief); 11,1% van de door de patiënt gerapporteerde inhalaties werd niet geregistreerd door het EIMD. Een mogelijke oorzaak hiervoor lag in de bluetooth verbinding tussen het EIMD en de mobiele telefoon.

Over het algemeen beschouwden patiënten de EIMD als acceptabel en gemakkelijk te gebruiken, maar velen aarzelden om het gebruik ervan voort te zetten in de toekomst. De herinneringsfunctie en de motiverende berichten werden niet door alle gebruikers gewaardeerd en de patiënten wilden graag dat de functies in de applicatie meer op hun persoonlijke wensen werden afgestemd.

**Hoofdstuk 8** vat de bevindingen van de onderzoeken samen en plaatst deze in een breder perspectief. Voor de meerderheid van de patiënten zal standaard zorg voldoende zijn. Er zijn echter kansen voor apothekers om patiënten te identificeren die aanvullende farmaceutische zorg nodig hebben. Hiervoor is belangrijk dat apothekers voldoende aandacht besteden aan het uitvragen van relevante informatie bij de patiënt. Zij dienen advies te geven, dat is gericht op de individuele behoeften en voorkeuren, in plaats van alleen standaard informatie te verstrekken. Ook bij de medicatiebewaking is het belangrijk om rekening te houden met individuele risicofactoren en patiëntvoorkeuren, zodat deze factoren onderdeel kunnen zijn van de geïntegreerde risicobeoordeling. Apothekers moeten de aanbevelingen van professionele richtlijnen niet te rigide toepassen, maar deze gebruiken als uitgangspunt voor een patiëntgerichte benadering en situationeel handelen. Het gebruik van kwaliteitsindicatoren is nuttig om de verbetering van processen op populatieniveau te volgen. Aan de huidige indicatoren dienen uitkomstenmaten toegevoegd te worden, die de geïndividualiseerde toepassing van de richtlijnen weerspiegelen.

Samengevat bevinden apothekers zich, in samenwerking met andere eerstelijns zorgprofessionals, in een goede positie om patiënten te identificeren die meer behoefte hebben aan zorg (bijvoorbeeld vanwege onvoldoende ziektecontrole of lage therapietrouw) en om interventies op maat aan te bieden. Ze hebben kansen om patiënten te begeleiden in de belangrijke periode kort na de start met nieuwe chronische medicatie. Ook kunnen zij patiënten identificeren waarbij de ziektecontrole in de loop van de tijd vermindert. Daarnaast kunnen apothekers patiënten ondersteunen in de verbetering van hun zelfmanagementvaardigheden. We hebben twee mogelijke hulpmiddelen beschreven voor proactieve patiëntmonitoring, die in aanvulling op afleverdata kunnen worden gebruikt voor het inzetten van tijdige interventies: regelmatig gebruik van de CARAT-vragenlijst en een EIMD. Deze hulpmiddelen kunnen worden gebruikt als diagnostisch hulpmiddel om patiënten te identificeren die zorg nodig hebben, maar ook om de effecten van een op maat gemaakte interventie te volgen. Alle componenten van elke interventie moeten echter kritisch worden beoordeeld op bruikbaarheid en patiënten moeten opties krijgen voor individualisatie, in overleg met hun zorgverlener.

Het is belangrijk om te onderzoeken wat de barrières en faciliterende factoren zijn van apothekers en apothekersassistenten met betrekking tot de toepassing en naleving van professionele richtlijnen en hun vermogen om aanbevelingen te individualiseren (bijvoorbeeld communicatievaardigheden en klinisch redeneren). In toekomstig onderzoek moet daarnaast worden gekeken naar het potentiële voordeel en de kosteneffectiviteit van individuele, op maat uitgevoerde interventies van apothekers en de effecten op klinische uitkomsten bij de patient.

# Dankwoord

Met het schrijven van dit dankwoord, komt er een einde aan een periode van 5 jaar. In 2014 kwam dit promotietraject op mijn pad; er stond een vacature in het Pharmaceutisch Weekblad, precies op het moment dat ik wel open stond voor verdieping van mijn werk in de apotheek. Ik had zin in deze nieuwe uitdaging, maar ik vond het tegelijk ook spannend; de onderzoekswereld was echt nieuw voor mij. Als je er net aan begint, lijkt de afronding van het proefschrift nog heel ver weg. Maar wat is de tijd snel gegaan en wat is er veel gebeurd in de afgelopen jaren. Ik heb me verder kunnen ontwikkelen, veel nieuwe ervaringen opgedaan en enorm veel geleerd. Ik had dit echter niet kunnen bereiken zonder de hulp van heel veel mensen. Allereerst wil ik mijn promotieteam bedanken voor alle hulp en het vertrouwen dat ze in mij hadden.

Peter, ik heb veel geleerd van jouw ervaringen, inzichten en ideeën. Ik bewonder je kritische blik en ik ben je dankbaar voor je betrokkenheid en begeleiding. Al tijdens één van onze eerste besprekingen gaf je aan dat ik me vooral geen zorgen moest maken als die publicaties niet zo snel gerealiseerd zouden worden als ik zou willen. Ook in de jaren daarna heb je mij regelmatig laten weten wél het vertrouwen te hebben in de voortgang en een goede afronding, vaak op de momenten wanneer het mij juist aan dat zelfvertrouwen even ontbrak.

Michel, ik heb veel geleerd van jouw pragmatische insteek; je nuchtere kijk op veel dingen was erg verhelderend. Toen ik eens behoorlijk negatieve commentaren kreeg op een ingestuurd artikel, reageerde jij dat reviewers ook wel eens een slechte dag hebben. Het hielp mij om de commentaren meer te relativeren, er de nuttige zaken uit te halen en het vooral gewoon weer ergens anders te proberen. Het was fijn dat je deel uitmaakte van mijn begeleidingsteam; je kijkt echt met een andere blik naar de apotheekpraktijk. Jouw perspectief heeft mij veel nieuwe inzichten gegeven, veel dank daarvoor.

Martina, dank je wel voor je tomeloze energie en nieuwe ideeën. Je gaf me veel mogelijkheden om me verder te ontwikkelen; je stimuleerde het volgen van diverse cursussen, zorgde dat er mogelijkheden waren om congressen en symposia te bezoeken en je bracht me in contact met veel mensen uit je netwerk. Na alle werkplek-wisselingen, waren er voor mij steeds minder directe collega's met wie ik dingen kon bespreken. Veel van mijn vragen kwamen dan ook bij jou terecht en je was altijd bereid me te helpen wanneer dit nodig was. Ik ben je dankbaar voor deze ondersteuning en alle feedback die je me hebt gegeven.

Ik wil ook de overige coauteurs bedanken voor hun bijdragen aan de publicaties: Charlotte Poot, Niels Chavannes, Elaine Wong-Go en Berry Daemen. Daarnaast een woord van dank aan de leden van de manuscriptcommissie. Prof. Dr. Van Dulmen, Prof. Dr. Assendelft en Prof. Dr. Van Dijk, hartelijk dank dat jullie bereid waren tijd vrij te maken om mijn manuscript te beoordelen.

Graag wil ik AstraZeneca bedanken voor hun ondersteuning. Andrea Sellink, Anouk Veldman, Denise de Bondt, Hannie de Munnik, Jurre Keijzers, Mieke Bastiaanse, Victor Schild en Wendy Beekman; bedankt voor de inspirerende brainstormsessies en de zorgvuldigheid waarmee jullie omgingen met alle resultaten uit dit traject. Fantastisch dat jullie ook betrokken zullen blijven bij het vervolgtraject!

Het promoveren naast een baan als beherend apotheker bracht ook wat organisatorische uitdagingen met zich mee. Naast het feit dat ik 2 dagen per week niet in de apotheek aanwezig was en dit moest worden opgevangen, waren er zeker in de eerste jaren regelmatig cursusdagen of andere verplichte activiteiten. Helaas werd een congres, cursus of symposium niet uitsluitend georganiseerd op de vaste dagen die ik had ingepland voor het onderzoek. Dit heeft het nodige gevraagd van mijn werkgever en collega's. Hiervoor ben ik hen dankbaar. Een speciaal woord van dank voor Jan en Diederik. Jullie stonden er vanaf het begin voor open dat ik mijn baan in de apotheek zou gaan combineren met onderzoek en jullie hebben mij alle praktische mogelijkheden en ondersteuning geboden om hiermee te starten.

Graag wil ik ook de collega's van mijn intervisiegroep bedanken; het is fijn om met elkaar te kunnen spreken over allerlei zaken die spelen. Dank voor jullie interesse en adviezen. Daarnaast vond ik het altijd heel waardevol om ervaringen uit te wisselen met andere apotheker-onderzoekers die een baan in de openbare apotheek combineerden met onderzoek. Sanne, Bram, Sek-Hung en Jamila; het was leuk om jullie regelmatig tegen te komen op verschillende congressen of symposia en bij te praten over onze onderzoeken. Bedankt voor jullie belangstelling en alle leuke gesprekken.

Praktijkonderzoek kan natuurlijk ook niet uitgevoerd worden zonder medewerking vanuit de praktijk. Ik wil graag een woord van dank uitspreken naar alle personen die aan onze onderzoeken hebben meegewerkt: masterstudenten farmacie vanuit de Universiteit Leiden, de groepen met Apiossen, apothekers, farmaceutisch consulenten, apothekersassistenten en andere medewerkers. Een speciaal woord van dank voor Annemarie, Antine, Barbara, Güler, Helma, Jamila en Martika; bedankt voor jullie hulp bij SMARAGD en bij de interviews.

Mariska van der Ham; je bent bij veel van onze studies betrokken geweest; bedankt voor al je praktische hulp bij het verwerken van gegevens in Questback en bij de intensieve follow-up periode van SMARAGD. Wat een klus was het om elke 2 weken een herinnering te versturen naar de patiënten uit de interventiegroep om de vragenlijst in te vullen en de resultaten van deze vragenlijst dan weer te verwerken en aan hen terug te koppelen. Het was fijn om hierbij hulp te krijgen. Ellen en Kim, bedankt voor jullie hulp met het transcriberen van de interviews.

Uiteraard ook een woord van dank aan alle patiënten die hebben meegedaan aan onze studies; jullie hebben tenslotte alle vragen beantwoord, vragenlijsten ingevuld

en ervaringen gedeeld. Zonder jullie medewerking was dit proefschrift niet tot stand gekomen.

Als externe promovendus was ik verbonden aan IQ Healthcare. In de eerste jaren was ik nog regelmatig, in ieder geval op woensdag, in Nijmegen te vinden. Het was niet altijd zo gezellig dat onze flexkamer ineens was omgedoopt tot stiltekamer, maar de lunchwandeling in het park was een welkome afwisseling. Marjo, Mireille en Willemijn; dank voor de leuke tijd. Caroline, fijn dat er een mogelijkheid was om één van de onderzoeken te laten uitvoeren binnen de vervolgopleiding. Dank voor je hulp hierbij en daarnaast voor al je belangstelling; het was fijn om ervaringen te kunnen uitwisselen. Tim, jou wil ik nog in het bijzonder noemen. Je had hetzelfde begeleidingsteam en doordat jij al eerder was gestart, liep je altijd een stuk voor op mij. De meeste vragen stelde ik dan ook aan jou en je maakte tijd om deze te beantwoorden en ideeën uit te wisselen. Tijdens de congressen was had je jezelf de mooie taak gegeven om elke deur voor me open te houden, en dit mis ik uiteraard wel sinds je zelf je traject hebt afgerond. Je bent nog altijd belangstellend, dank je wel daarvoor.

Noortje, wij als externe promovendi waren duidelijk niet altijd goed op de hoogte van alle procedures en het viel ook niet altijd mee om de verplichte cursussen goed in te plannen in de volle agenda's. Gelukkig ontmoette ik jou al bij de introductiecursus en we kwamen daar tot de ontdekking dat we verbonden waren aan dezelfde afdeling. Daarna maakten we er gewoon steeds een gezellig uitje van. Veel succes bij de afronding van jouw promotie!

Mijn lieve familie, vrienden en vriendinnen, bedankt voor het luisteren naar mijn verhalen. Mama, John, papa, Marian, Judith, Bart, Arjen, Manon, Matthijs en Marlot; dank je wel voor jullie steun en belangstelling, ook als jullie soms (of vaak) geen idee hadden waarmee ik nu precies bezig was. Ik realiseer me dat ik vaak meer vertelde over het proces, dan over de inhoud. Juud, natuurlijk een speciaal woord van dank voor jou. Wat fijn dat jij mijn paranimf wilt zijn. Ik ben blij met een zus als jij. Je wilde echt al mijn artikelen lezen, en je was soms nog trotser dan ikzelf als er één geaccepteerd werd. Je hielp mij om alles meer in perspectief te zien en niet alleen te focussen op het eindresultaat, maar ook vooral te genieten van de tussenstappen.

Lieve Peter, zonder jou was ik hier niet aan begonnen. We hebben vooraf uitgebreid gesproken over de consequenties en je stond altijd achter mij. Zonder jou had ik het ook niet kunnen afronden. Jij hebt absoluut het meeste last gehad van mijn frustraties of twijfel als er weer eens iets niet liep zoals ik het graag wilde, maar ook op die momenten was je er. Dank je wel voor je geduld en dat je er altijd voor mij bent. Ik kijk uit naar onze bruiloft en alle tijd die vrij komt voor ons samen.

# About the author

Esther Kuipers was born 9 May 1986 in 's-Hertogenbosch, the Netherlands. In 2004 she completed secondary school at the Willem van Oranje College in Waalwijk. Subsequently, she studied Pharmacy at Utrecht University in Utrecht. She obtained her Master of Science degree in Pharmacy in 2010. She started working in December 2010 at the cluster of pharmacies in Rosmalen, Berlicum and Empel, which she combined with the 2-year post-academic advanced community pharmacist education program. In December 2012 she was registered as a community pharmacist. She became managing pharmacist at Apotheek Empel. Since September 2014 she combined her work as community pharmacist with her PhD research, affiliated to the department of IQ Healthcare, Radboud Institute for Health Sciences of the Radboud University in Nijmegen. From July 2016 to July 2019 she worked as managing pharmacist at BENU Apotheek Zeist West in Zeist. Since 2017, she is a member of the Special Interest Group "Lung diseases" of the Royal Dutch Pharmacists Association (KNMP). After completing this PhD, she aims to continue her work as a community pharmacist, combined with pharmacy practice research.

# List of co-authors


## Prof. Dr. NH Chavannes

- Department of Public Health and Primary Care, Leiden University Medical Centre, Leiden, The Netherlands.

## Dr. BJG Daemen

- Royal Dutch Association for the Advancement of Pharmacy (KNMP), Guideline development, The Hague, The Netherlands.

## CC Poot, MSc

- Department of Public Health and Primary Care, Leiden University Medical Centre, Leiden, The Netherlands.

## Prof. Dr. PAGM de Smet

- Department of Clinical Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands.
- Department of IQ Healthcare, Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands.

## Dr. M. Teichert

- Department of Clinical Pharmacy & Toxicology, Leiden University Medical Centre, Leiden, The Netherlands.

## Prof. Dr. M. Wensing

- Department of General Practice and Health Services Research, University Hospital Heidelberg, Heidelberg, Germany.
- Department of IQ Healthcare, Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands.

## E Wong-Go, MSc

- Royal Dutch Association for the Advancement of Pharmacy (KNMP), Guideline development, The Hague, The Netherlands

# List of publications

## International publications presented in this thesis

1. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Self-management research of asthma and good drug use (SMARAGD study): a pilot trial. Int J Clin Pharm. 2017 Aug;39(4):888-896.
2. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Considerations of prescribers and pharmacists for the use of non-selective β-blockers in asthma and COPD patients: An explorative study. J Eval Clin Pract. 2018 Apr;24(2):396-402.
3. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Barriers and facilitators for community pharmacists' participation in pharmacy practice research: a survey. Int J Pharm Pract. 2019 Aug;27(4):399-402.
4. Kuipers E, Poot CC, Wensing M, Chavannes NH, De Smet PAGM, Teichert M. Self-Management Maintenance Inhalation Therapy With eHealth (SELFIE): Observational Study on the Use of an Electronic Monitoring Device in Respiratory Patient Care and Research. J Med Internet Res. 2019 May 30;21(5):e13551.
5. Kuipers E, Wensing M, Wong-Go E, Daemen BJG, De Smet PAGM, Teichert M. Adherence to guideline recommendations for asthma care in community pharmacies: actual and needed performance. NPJ Prim Care Respir Med. 2019 Jul 11;29(1):26.
6. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Exploring patient's perspectives and experiences after start with inhalation maintenance therapy: a qualitative theory-based study. Submitted.

## Other publications

1. Mets MA, Kuipers E, de Senerpont Domis LM, Leenders M, Olivier B, Verster JC. Effects of alcohol on highway driving in the STISIM driving simulator. Hum Psychopharmacol. 2011 Aug;26(6):434-9.
2. de Haan L, Kuipers E, Kuerten Y, van Laar MW, Olivier B, Verster JC. The RT-18: a new screening tool to assess young adult risk-taking behavior. Int J Gen Med. 2011;4:575-84.
3. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Onderzoek naar zelfmanagement bij astma en goed geneesmiddelengebruik (SMARAGD-studie): een pilotonderzoek. Nederlands Platform voor Farmaceutisch Onderzoek. 2018;3:a1667.
4. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Onderzoek naar zelfmanagement bij astma en goed geneesmiddelengebruik (SMARAGD-studie): een pilotonderzoek. Nederlands Tijdschrift voor Allergie & Astma 2018;18:112-122.
5. Kuipers E, Wensing M, De Smet PAGM, Teichert M. Inzicht in meerwaarde motiveert apotheker tot praktijkonderzoek. Pharmaceutisch Weekblad 2019; 29/30: 14-15.

# Data management

For each study of this thesis involving participant data, the research protocol was submitted to the local Medical Ethics Committee CMO Arnhem-Nijmegen. All studies were officially declared exempt from ethical approval for human subjects research. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data from chapter 2, 3, 5, 6 and 7 were collected by pharmacists, or pharmacy students in cooperation with their supervising pharmacists during their educational internships. No identifying patient information was shared with the researchers. The written informed consent forms were stored in the pharmacy. Recordings of the interviews were deleted, only the anonymized transcripts were saved.

For chapter 6, patients completed paper questionnaires at study start and study end (6 months). As a result of the intensive cooperation with the Department of Clinical Pharmacy and Toxicology of the Leiden University Medical Centre, these paper data were stored in the department archive in Leiden (LUMC, KFT room 009). All paper data were entered into the computer by use of Microsoft Excell. An audit trail was incorporated to provide evidence of the activities that has altered the original data. Data where converged from Excell to SPSS (SPSS Inc., Chicago, Illinois, USA).

The survey and questionnaire data described in chapters 2, 3, 4 and 7 were collected via a secure version of Questback, and data collected in chapter 7 via a secure platform of Box. No identifying information was collected in the questionnaires. The privacy of the participants in all studies is warranted by use of encrypted and unique individual subject codes. This code was stored separately from the study data, by the participating healthcare professionals.

Until chapter 5 of this thesis has been published, the raw and processed data and accompanying files (descriptive files, transcripts, etc.) will be stored in a personal folder on the department server of IQ healthcare which is accessible only by the main researchers of this project. Thereafter, the data will stored on the secured IQ healthcare archive server in a folder called “Farmaceutische zorg bij longaandoeningen” for 10 years, which is accessible only by the secretary of IQ healthcare. To ensure interpretability of the data, all primary and secondary data, descriptive files, research protocols and scripts used to provide the final results are documented along with the data. Since the participants of the studies did not provide informed consent for sharing their data publically, requests for data can be made via receptie.iqh@radboudumc.nl. A suitable way to share the data will then be sought.

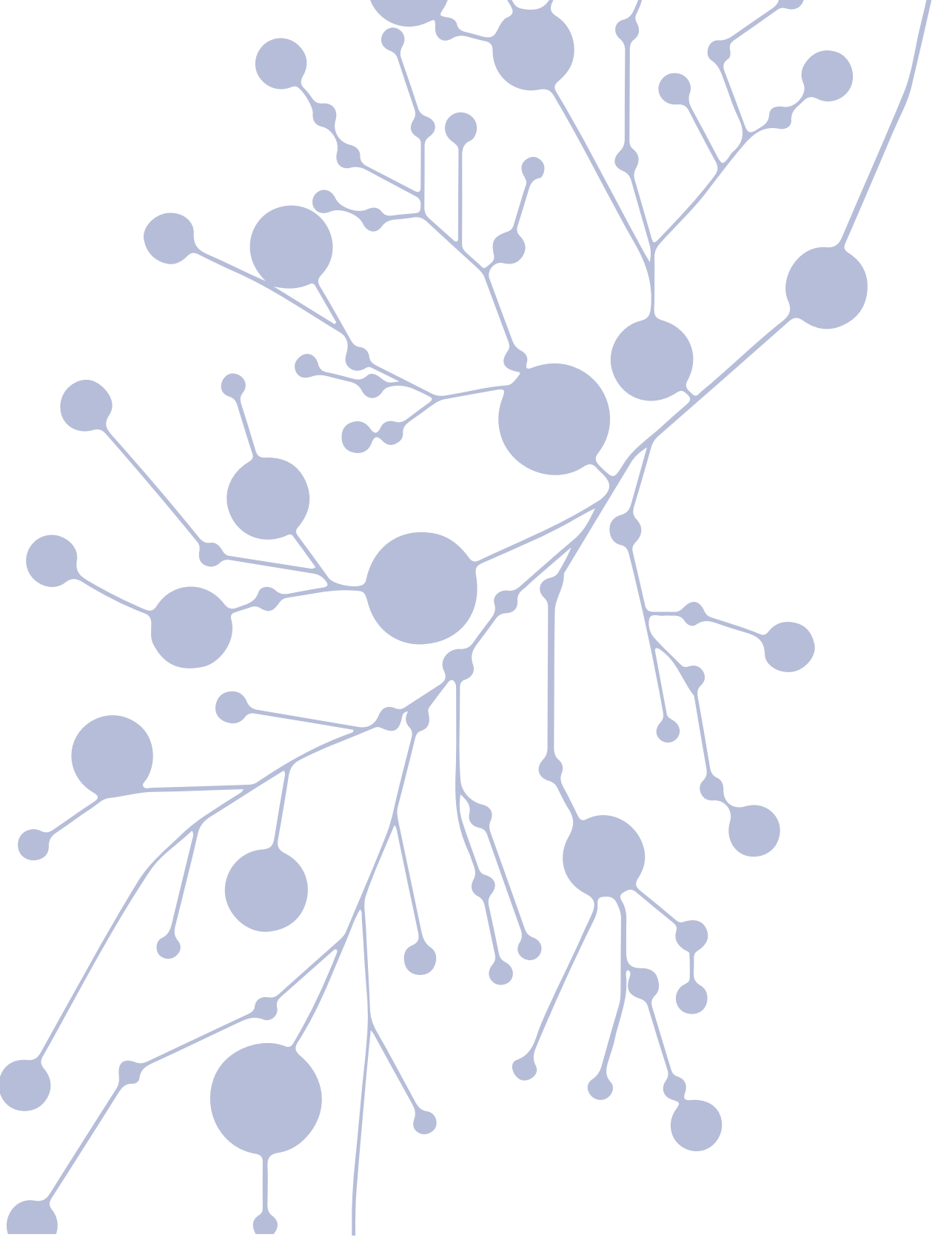
# PhD Portfolio

Institute for Health Sciences
Radboudumc

| | |
|---|---|
| *Name PhD candidate: E. Kuipers*<br>*Department: IQ Healthcare*<br>*Graduate School: Radboud Institute for Health Sciences* | *PhD period: 1-9-2014 –1-10-2019*<br>*Promotors: Prof. P.A.G.M. de Smet, Prof. M. Wensing*<br>*Co-promotor: Dr. M. Teichert* |

| | Year(s) | ECTS |
|---|---|---|
| ***TRAINING ACTIVITIES*** | | |
| ***a) Courses & Workshops*** | | |
| - R01: Basiscursus SPSS, EpidM | 2014 | 0,5 |
| - Digitale tools (Pubmed), Radboud University | 2015 | 0 |
| - V10: Epidemiologisch onderzoek: opzet en interpretatie, EpidM | 2015 | 2,5 |
| - V20: Principes van epidemiologische data-analyse, EpidM | 2015 | 2 |
| - Academic Writing, Radboud University | 2015 | 3 |
| - Introduction Course, RIHS | 2016 | 1 |
| - Perfecting your academic writing skills, Radboud University | 2016 | 1,5 |
| - V30: Regressietechnieken, EpidM | 2016 | 2,5 |
| - K73: Longitudinale data-analyse, EpidM | 2016 | 1,5 |
| - K74: Multilevel analyse, EpidM | 2016 | 1 |
| - BROK course for Good Clinical Practice (certificate) | 2017 | 1,5 |
| - K78: Kwalitatief onderzoek, EpidM | 2017 | 1 |
| - K72: Doelmatigheidsonderzoek: methoden en principes, EpidM | 2017 | 1 |
| - V40: Klinimetrie, EpidM | 2017 | 1,5 |
| - Scientific Integrity, RIHS | 2017 | 1 |
| - V50: Praktische epidemiologie: opzetten van een onderzoek, EpidM | 2018 | 4 |
| ***b) Seminars & lectures*** | | |
| - KNMP Regiobijeenkomst: Therapietrouw; u maakt het verschil | 2015 | 0,1 |
| - Allergische rinitis en astma | 2015 | 0,1 |
| - COPD-behandeling anno 2015; Roken: gevolgen en hulp bij stoppen | 2016 | 0,1 |
| - KNMP Regiobijeenkomst: MFB's | 2017 | 0,1 |
| - Workshop KNMP Najaarscongres: Re-envisioning patient education about their maintenance therapy | 2018 | - |

| | | |
|---|---|---|
| ***c) Symposia & congresses*** | | |
| - KNMP congres: Farmacogenetica | 2015 | 0,2 |
| - Prisma symposum: Farmaceutisch praktijkonderzoek | 2015 | 0,2 |
| - ESCP congres Lissabon: Medicines information – making better decisions (poster presentation) | 2015 | 1 |
| - KNMP congres: Therapietrouw | 2015 | 0,2 |
| - KNMP congres: Palliatieve zorg | 2016 | 0,2 |
| - Prisma symposium: Farmaceutisch praktijkonderzoek (oral presentation) | 2016 | 0,2 |
| - CArE days Eindhoven | 2016 | 0,2 |
| - PCNE Working Conference Bled, Slovenia (1x oral and 2x poster presentation) | 2017 | 1 |
| - KNMP congress: Precision Medicine: what's in it for the pharmacist?' | 2017 | 0,2 |
| - Healthcare Experience Domburg (oral presentation) | 2017 | 0,2 |
| - Longdagen (2x oral and 2x poster presentation) | 2017 | 0,2 |
| - Prisma symposium: Farmaceutisch praktijkonderzoek (2x oral presentation) | 2017 | 0,2 |
| - ESCP Meeting Leiden | 2017 | 0,5 |
| - KNMP congres: Vizier op de nier | 2017 | 0,2 |
| - ESCP Congres Heidelberg: Sciense meets practice, towards evidence-based clinical pharmacy services (2x poster presentation) | 2017 | 0,8 |
| - VJA-Optima Farma Patientendag: Ouderdom komt met gebreken | 2018 | 0,2 |
| - KNMP congres: Patient power | 2018 | 0,2 |
| - Prisma symposium: Farmaceutisch praktijkonderzoek (oral presentation) | 2018 | 0,2 |
| - KNMP congres: Maag Darm Lever | 2018 | 0,2 |
| - PCNE Congres Egmond aan Zee (2x poster presentation) | 2019 | 0,8 |
| - KNMP congres: Oncologica | 2019 | 0,2 |
| - Prisma symposium: Farmaceutisch praktijkonderzoek (2x oral presentation) | 2019 | 0,2 |
| ***d) Other*** | | |
| - Member special interest group lung diseases KNMP | 2017-present day | |
| ***TEACHING ACTIVITIES*** | | |
| ***e) Lecturing*** | | |
| - Workshop SELFIE, University of Leiden. | 2018 | 0,2 |
| ***f) Supervision of internships / other*** | | |
| - Supervision internship eHealth, University of Leiden | 2018 | 0,5 |
| ***TOTAL*** | | **34.1** |



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