Supporting patients:
pharmacy based interventions to improve medication adherence

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

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Supporting patients: pharmacy based interventions to improve medication adherence

Begeleiding van patiënten:
interventies van apothekers om therapietrouw te verbeteren

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 9 september 2015 des middags te 2.30 uur

door

Marcel Jan Kooij

geboren op 1 april 1978 te Enschede

Promotor: Prof. dr. M.L. Bouvy

Copromotoren: Dr. E.R. Heerdink
Dr. ir. L. van Dijk

‘De man die bergen verzet heeft,
begon met het verplaatsen van één steen’

Chinees spreekwoord

Voor mijn ouders

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CHAPTER 1

Introduction

Introduction

Adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behaviour - taking medication - corresponds with agreed recommendations from a health care provider".[1] Adherence to any therapeutic recommendation, including prescribed medication, has been reported to be low.[1-3] The WHO estimates that in developed countries 50% of patients with a chronic disease do not fully adhere to treatment. Non-adherence to long-term medication therapies severely compromises the effectiveness of treatment and is critical from both the perspective of quality of life of individual patients and from the perspective of public health and health economics. Low adherence to for example cardiovascular medication is both associated with higher risk of death due to cardiovascular disease[4,5] and with increased health care costs due to preventable hospitalisations related to cardiovascular complications.[6,7] Similarly, non-adherence to antidepressants can lead to a lower quality of life for the patient and to increased sick leave.[8]

Medication adherence can be divided in three phases: initiation, implementation and discontinuation[9] (Figure 1). The initiation phase ends with the decision of the patient to take the first dose. In the next phase, the patient starts implementing the therapy and adherence in this phase can be described as the extent to which a patient's actual intake behaviour corresponds to the prescribed dosing regimen. At any moment in time the therapy can be discontinued which is marked by the intake of the last dose. Discontinuation can be abrupt but can also be preceded by a phase for example when medication is tapered.[10] Persistence is defined as the length between initiation and the last dose taken.

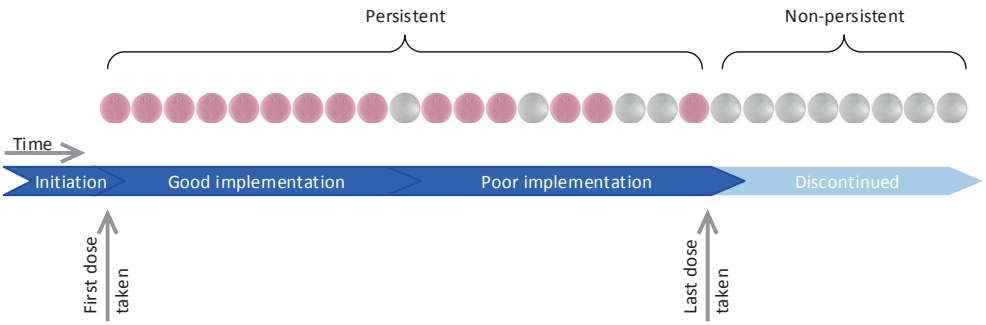

Figure 1: Illustration of the phases of medication adherence (adapted from Vrijens at al.[9]).

Although non-adherence can compromise the effectiveness of a treatment, researchers and health care professionals tend to forget that a patient can only be non-adherent when there are mutually agreed recommendations. Technically if a patient does not agree with

the treatment, a patient cannot be non-adherent. This seems a semantic discussion, however it stresses the role of the patient in accepting or rejecting treatment and that the patient has to be able to make an informed decision.

Given the crucial role of adherence in achieving positive outcomes of therapy, numerous initiatives have been started to study and improve adherence. However, interventions to improve adherence show inconsistent results and several experts have called for more effective interventions and studies with sufficient power that show the value of these interventions.[11,12] Moreover interventions should be feasible to implement in daily clinical practice and have to be cost-effective. In light of the extent of the problem, it has been suggested that simple and feasible interventions, preferably in a multidisciplinary setting, are most promising.[12]

Factors associated with non-adherence

Adherence is influenced by numerous factors.[1,13-19] The WHO categorised factors influencing non-adherent behaviour in five dimensions: socio-economic related factors, health care team and system-related factors, condition-related factors, therapy-related factors and patient-related factors.[1] A review of reviews identified 771 factors related to adherence and categorised the factors in the five dimensions confirming that non-adherence indeed is a multifaceted problem.[13] For example, lack of presence of symptoms (condition) has a negative effect on adherence[20-23] while patient involvement in decision making (health system) has a positive effect.[23-25] Cognitive impairment, low attention and working memory (patient) have a negative effect[26-29] while low dosing frequency (therapy) has a positive effect.[21,22,29]

Non-adherence (and adherence) can be intentional or unintentional. Intentional non-adherence refers to purposefully not taking the medication as prescribed. An example of an intentional reason can be that a patient decides that the benefits of a treatment do not outweigh the risks or downsides. Forgetfulness is an obvious example of unintentional non-adherence. Although this distinction is helpful, it can be a simplification of real life, since for example concerns about medication are related to forgetfulness and carelessness in taking medications.[16] An alternative approach is suggested by Kane and Robinson et al.[30] dividing barriers to adherence into practical barriers and perceptual barriers. Examples of practical barriers are cost of treatment, memory barriers, daily routine barriers (e.g. inconvenience of the medical regimen). Perceptual barriers relate to patients' attitude towards the therapy like lack of belief in the necessity or presence of concerns about for example side effects. Perceptual barriers are based on an internal negotiation between the perceived necessity and any concerns relating to it.[31] A framework to quantify patients' beliefs is the "Necessity-Concerns Framework" (NCF).

Basis for this framework are patients' beliefs about medication which can be grouped under two categories: perceptions of personal need for treatment (necessity beliefs) and concerns about a range of potential adverse consequences.[32] It has been shown that higher necessity beliefs and lower concerns are associated with higher adherence.[14,16,32-34] Patients' beliefs are influenced by factors on all five dimensions. For example the nature of the disease (condition) will have an influence on patient beliefs as will support from the physician (health system) and opinion and experiences of family (social).

Promoting adherence

Since numerous factors influence adherence, most of the interventions that are effective in improving adherence are multifaceted[11,12,35-37] and involve a combination of strategies such as education, simplifying the regimen,[38] motivation and providing reminders.[39,40]

As Osterberg et al. suggested, three domains are important in the improvement of adherence: 1) patients; 2) health care providers; and 3) health care practices.[2,41] The first domain, is the patient with his/her own specific beliefs and clinical and educational needs. The second domain is the domain of the health care providers including physicians, pharmacists, nurses and other allied health care professionals. The third domain includes health care practices and also the health care system.

Figure 2 presents these three domains including examples of issues relevant to adherence.

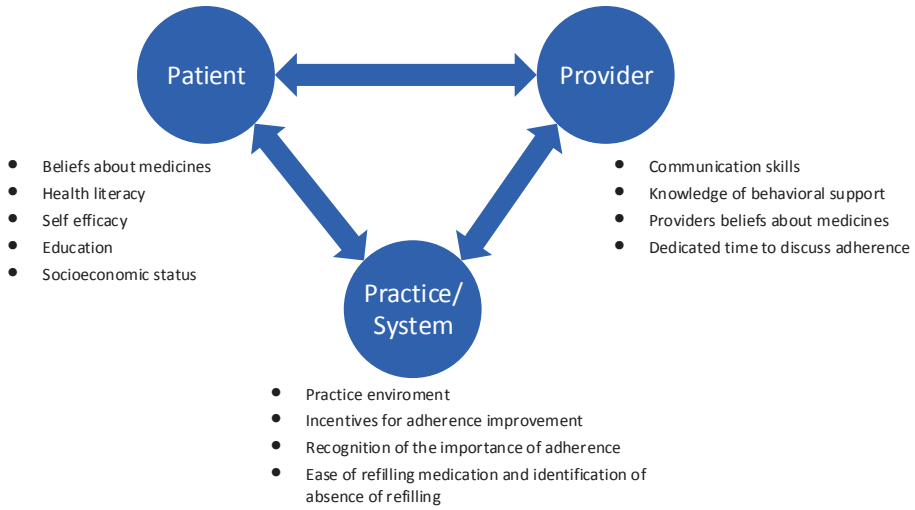

Figure 2: Examples of issues to address when improving adherence both from the perspective of the patient, the health care provider and practice/health care system (adapted from Osterberg et al.,[2] Mendys et al.[41] and Desai et al.[42]).

Although interventions to improve adherence can focus on one domain, other domains can have an impact as well and should thus be taken into account. For example, if pharmacists are trained to deliver additional interventions, the system simultaneously has to provide incentives to deliver these interventions. Relations between domains are important as well. For example, trust between patient and health care provider is likely to improve adherence.[17,43] Moreover, to reach optimal results, health care providers should tailor their services to individual patients' needs. A helpful model to guide providers in the development of these services is proposed by DiMatteo et al: the Information-Motivation-Strategy (IMS) model.[44] The information component stresses the importance of knowledge of the patient about how and why to use the medication. Patients need information about their medication to support appropriate and safe use.[45-49] This may include practical instructions but also information about possible side effects, the expected pharmacological action or instruction on how to act in specific circumstances such as the accidental missing of a medication intake moment.[46,50,51] This information should improve patients' understanding of the expected benefits and downsides/risks of treatment with medication.[32,47] Health care providers should assess if a patient understands the information, and is able to appraise and use this information.[52] Knowing how and why to take medication is not enough. In addition, patients have to be motivated to integrate the prescribed medication regimen in their daily routine. Health care providers have the responsibility to assess patients' motivation to implement treatment recommendations and to assess perceptual barriers that may negatively influence adherence to medication.[31] Practical barriers can also impede adherence[53] including limited self-efficacy. Health care providers need to identify these issues as well and can help to find a strategy such as the provision of reminder devices,[13] a simplification of the dosing regimen or help patients find a way to integrate the regimen into the daily routine.

Current practice in improving adherence

Health care providers including pharmacists have tools at their disposal for improving adherence. These include providing information, providing counselling including motivational interviewing, monitoring adherence and providing reminder aids. However, it has been frequently shown that many patients do not receive optimal care. Studies show that patients' information needs are not always met,[50,51,54,55] that counselling from either physicians[56] or pharmacists[57-59] is not sufficient, that barriers to adherent behaviour are not always assessed[31,60,61] and that the quality of communication is not optimal.[62,63] Despite evidence that the majority of patients believe that communicating with their health care provider about their medication is useful, providers themselves find if often

difficult to discuss adherence.[64,65] Additionally, clinical guidelines often lack attention on adherence to medication.[66]

Numerous factors can impair implementation of adherence promoting activities in daily practice. These factors can be either related to the patient, the health care provider or the practice/health care system. Lack of interest of the patient can be a hampering factor. Also language problems, low literacy skills and physical constraints can be reasons from the patient perspective that the provided care is not optimal. Lack of knowledge, communication skills or experience can be hampering factors at the level of the health care provider. Lack of stimuli provided by the health care system such as remuneration or technical support can influence implementation of adherence promoting activities.

Role of the pharmacist

Over the past decades, the pharmacist's role in health care has changed dramatically. Reinforced by regulations, schools of pharmacy and pharmacy associations, pharmacist-patient communication is now considered an integral aspect of pharmacist provided services.[67] These services are part of the Medication Therapy Management Services (MTMS). MTMS have three important goals: (1) providing education and counselling to improve patients' understanding of their medication; (2) improvement of medication adherence and (3) detection of adverse drug reactions and patterns of improper prescription medication use.[68]

Pharmacy practice guidelines generally recommend to provide counselling[41,57,69] about benefits and risk, correct use of medication and promoting adherence[54,70] but these guidelines are (not yet) fully implemented in daily pharmacy practice.[57,58,71-73] When medication is dispensed the first time, patients should receive written and oral information about the medication, therapy and instructions for use, including assessment of understanding the information and enactment of this knowledge. At the first refill prescription, pharmacists and their team should concentrate on discussing experiences patients have with their medication, including the practical and perceptual barriers patients encounter.

Pharmacists and their teams can also help in the implementation phase of a patient's therapy for example by recognising patients who do not return for a refill or return later than expected for a refill. Pharmacist should utilize the fact that they have frequent contact with patients, that they are easy accessible, well trained and educated.[45]

Objectives and outline of this thesis

Adherence to medication for chronic conditions is generally low and not using medication as intended can lead to treatment failure. Health care providers including pharmacists and their teams have a role in supporting patients to adhere. The overall aim of this thesis is to design and evaluate interventions in community pharmacies focussing on improving medication adherence both at the start of therapy and in the implementation phase. Moreover, we study frequency and nature of counselling in pharmacies and propose definitions and standardization for assessing adherence using dispensing data.

This thesis contains 6 chapters. **Chapter 2** provides an overview of current counselling practices in pharmacies using a quantitative study about the frequency and nature of counselling in pharmacies.

In **Chapter 3** we propose standardization to assess medication adherence using pharmacy dispensing records.

Chapter 4 and 5 describe innovative interventions aimed at improving adherence.

Chapter 4 focuses on an intervention for patients starting with medication using counselling by telephone to improve adherence, the Telephone Counselling Intervention by Pharmacist (TelCIP). **Chapter 4.1** delineates the TelCIP trial design. In **Chapter 4.2** we explore the implementation of the intervention and provide more information about the fidelity while **Chapter 4.3** contains the results of a qualitative study focussing on the content and quality of the communication used in the telephone counselling. In **Chapter 4.4** the intermediate effects of the intervention on patients' perception are presented. Finally in **Chapter 4.5** we describe the results of the intervention on patient adherence.

Chapter 5 contains the results of a three-armed intervention study that focussed on patients who were seemingly non-adherent with lipid lowering medication during the implementation phase. The use of an electronic reminder device (ERD) alone is compared with counselling combined with the use of an ERD as well as with usual care.

Chapter 6 contains a general discussion in which the results of these studies are summarized and put into a broader perspective. In this discussion we also provide recommendations for research and daily pharmacy practice.

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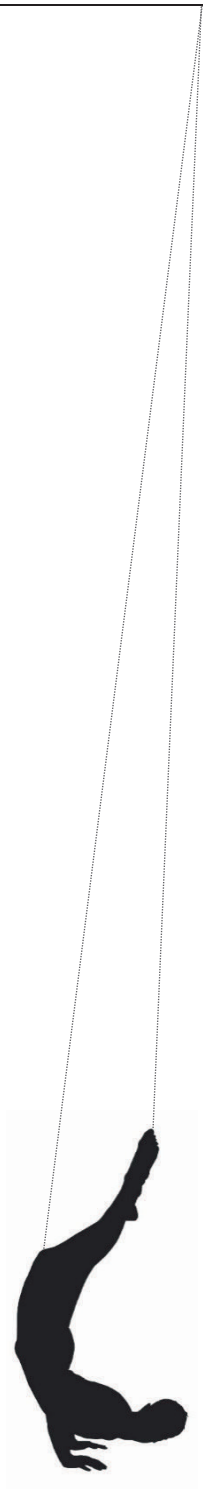

CHAPTER 2

Frequency, nature and determinants of pharmaceutical consultations provided in private by Dutch community pharmacists

Marcel J. Kooy, Wouter S. Dessing, Esther F. Kroodsma, Steven R.J.G. Smits, Esther Fietjé, Martine Kruijtbosch, Peter A.G.M. de Smet

Pharmacy World and Science 2007; 29: 81–89

Abstract

Objective: According to a report published by the federation of Dutch patients' associations, patients would like to see a pharmacist, who acts more as a personal adviser. This raised the question, how often Dutch community pharmacists have personal consultations with their patients in daily practice, on which factors this depends, and what kind of topics are discussed during these meetings.

Setting: Community pharmacies in the Netherlands.

Method: A questionnaire was distributed among 800 randomly selected pharmacies. Questions were restricted to consultations characterized by one-to-one-contact, drug therapy related content, and adequate privacy. These consultations were labelled as pharmaceutical consultations in private to distinguish them from other contacts between pharmacists and patients.

Main outcome measure: Number, content, and character of consultations.

Results: 198 (24.8%) community pharmacies responded. The pharmacists provide an average of roughly 1.2 consultations in private per working day. The vast majority of respondents provided face-to-face and telephone consultations (94.4 and 91.9%, respectively), only a minority gave consultations by e-mail (30.8%). These consultations primarily dealt with topics related to medication safety. The mean overall time spent was 290 min per month. A relatively high frequency of personal consultations was significantly associated with the absolute number of full-time equivalent pharmacists in the pharmacy.

Conclusion: The frequency of pharmaceutical consultations in private is low, but may be improved by reorganisation of the pharmacist's activities. The possibility of personal consultations by e-mail is not yet well developed. Further research is needed to assess the patient's view of pharmaceutical consultations in private.

Impact of our findings on practice:

- Dutch community pharmacists should consider reorganising their activities, in order to increase the number of pharmaceutical consultations in their pharmacies
- The possibility for pharmacy clients to have a personal consultation by e-mail should be further developed

Introduction

Some years ago, the Dutch Patients' and Consumers' Federation (which coordinates patients' associations in The Netherlands) published a report about the opinions of Dutch patients about the community pharmacist.[1] The report made clear that patients would like to see a community pharmacist, who acts more as a personal adviser, e.g., by offering consultations during office hours or home visits. Apparently this patients' need was not adequately met. We wondered how often Dutch community pharmacists have personal consultations with their patients in daily practice, on which factors this depends, and what kind of topics are discussed during these contacts. During literature review, we found numerous studies on patient education, pharmacist counselling and pharmacist consultations. However, these activities often remained ill-defined,[2] and/or were only assessed within the conceptual framework of an experimental program and/or for a specific type of professional behaviour. Examples are studies on the performance of pharmacist-managed medication reviews and the monitoring of repeat prescriptions[3,4] on counselling concerning medication adherence[5,6] or non-prescription treatments,[7,8] on the provision of pharmaceutical services for specific patient groups (e.g., patients with diabetes),[9-11] and on the preparation and execution of comprehensive pharmaceutical care plans.[12,13] Overall assessments of the nature and frequency of the personal patient consultations that are given by community pharmacists as part of their daily routine appeared to be scarce. Johnson et al.[14] compared the routine provision of pharmacist consultations to US outpatients with two experimental models: the so called Kaiser Permanente (KP) model, which consisted of targeted pharmaceutical care services to high-risk patients (identified by their drug use); and the State of California (SC) model which consisted of mandated patient consultation to all patients with a new or changed refill prescription. They found that the control group recorded problems much less often than the two experimental groups (20 and 10% of the SC group and KP group, respectively) and that two-thirds of the actions undertaken in the control group were not directed towards the patients themselves but to the prescribing physician.[15] Chen and Britten[16] analysed the content of personal consultations provided by UK community pharmacists, but this was a qualitative study of only 25 consultations, all of which took place within GP surgeries and in patients' homes. Bell et al.[17] reported an overall figure concerning the provision of patient consultations by community pharmacists in Northern Ireland, but they only provided a crude estimate without explaining what they precisely meant by patient consultation. We therefore decided to perform a quantitative questionnaire study that would explore the overall frequency, nature and potential determinants of personal consultations that Dutch community pharmacists give to their patients.

Methods

Working definition of pharmaceutical consultations in private

Many contacts between community pharmacists and their patients are so brief and/or lack so much privacy that there was a real risk that community pharmacists might overestimate their personal consultations or report on them inconsistently. We therefore developed an unequivocal working definition of personal consultations that was consistent with the reported patients' need.[1] To qualify as a personal consultation, a contact had to fulfil the following conditions:

- One-to-one contact between patient (or patient's representative) and pharmacist (i.e., not a pharmacist's technician or another staff member);
- Drug therapy related content (i.e., not concerning issues such as drug prices or incontinence care products);
- Adequate protection of privacy (i.e., contact not at the counter, but face-to-face in a separate room, by telephone or by e-mail).

To distinguish these consultations from other contacts between pharmacists and patients, we decided to designate them as 'pharmaceutical consultations in private'*.

Data collection

In March 2004, a questionnaire was distributed to 800 randomly selected community pharmacies from a total of 1,730 Dutch pharmacies. The questionnaire was pretested by eight community pharmacists, which resulted only in a few minor textual alterations. The questionnaire stated our working definition of a pharmaceutical consultation in private and emphasized the importance of filling in the questionnaire with this definition in mind. The questionnaire addressed: (section 1) general characteristics of the respondent and the respondent's pharmacy; (section 2) general characteristics of the face-to-face consultations in the pharmacy of the respondent; (section 3) specific details about the most recent face-to-face consultation given by the respondent (e.g. which specific drugs and drug aspects were discussed); (section 4) general characteristics of the consultations by telephone in the pharmacy of the respondent; (section 5) specific details about the most recent consultation by telephone given by the respondent; (section 6) general characteristics of the consultations by e-mail in the pharmacy of the respondent; (section 7) specific details about the most recent consultation by e-mail given by the respondent; (section 8) general opinions of the respondent about different aspects of pharmaceutical

*After our study had been performed, the coordinating federation of Dutch patients' associations published a second study report about quality assessment of community pharmacies from the patient's perspective. This report identified the fact that other patients may readily listen in when a conversation takes place at the counter as the most important issue that should be improved[22]

consultations in private (e.g., the appropriateness of our working definition). After 2 weeks a reminder was sent to all pharmacists, but no additional incentive was offered.

Data handling and analysis

All responses were entered into a Microsoft Access database and then transferred into SPSS for Windows. Noticeable differences between the study sample and national data were tested for statistical significance by a χ^2-test. The number and average duration of consultations in private per pharmacy were assessed on basis of the responses to section 2 (face-to-face), section 4 (telephone), and section 6 (e-mail). The extent of consultations in private per pharmacy (expressed in minutes) was subsequently calculated for each type of consultation and for the total of consultations. The specific drugs and subjects discussed in consultations in private were assessed on basis of the responses to section 3 (last face-to-face), section 5 (last telephone), and section 7 (last e-mail). The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification for 2004.[18] To evaluate whether the pharmacies giving a relatively high number of face-to-face consultations were different in certain respects from the other pharmacies, the responding pharmacies were divided into two groups: those in the uppermost quartile (each of which provided at least 27 face-to-face consultations per month) and all the other pharmacies (each of which gave less than 27 consultations per month). These two groups were subsequently compared with respect to a number of pharmacy characteristics that were primarily derived from the responses to section 1 (general characteristics) and section 8 (general opinions) of the questionnaire. Responses to questions about the way, in which the pharmacy drew the patients' attention to the possibility of a face-to-face pharmaceutical consultation (section 3) were also included in this comparison.

Results

Of 800 pharmacies mailed, 198 (24.8%) responded. The basic characteristics of the responding pharmacists and their pharmacies are listed and compared with national data in Table 1. The questionnaire was filled in significantly more often by the managing pharmacist (either the pharmacy owner or a managing employee) and the pharmacies of respondents had significantly more often an ISO compatible certificate (26.3 vs 7.8%).

Table 1: Characteristics of responding pharmacists and their community pharmacies in comparison to national data.

Pharmacist characteristics	Study sample (n=198)	Remaining[#] (n=2536)
Gender and age		
Female (%)	42.4	46.5[a]
Age (mean)	39.5	41.1[a]
Position in pharmacy	0.0	0.0
Managing owner (%)	45.5*	28.4[a]
Non-managing owner (%)	5.1*	29.7[a]
Managing employee (%)	37.4*	4.0[a]
Non-managing employee (%)	11.1*	38.1[a]
Pharmacy characteristics	**(n = 198)**	**(n = 1532)**
Patients		
Average number registered (range)	9600 (500–21000)	8700[b]
Pharmacists		
Average number (range)	2.2 (1–19)	2.0[a]
FTEs[¶] (range)	1.7 (0.5–10)	1.6[b]
Pharmacist's technicians		
Average number (range)	9.6 (1–24)	7.8[a]
FTEs[¶] (range)	6.8 (1–33)	5.8[b]
Patients per pharmacist		
Average number registered per FTE pharmacist[¶]	5600	5500[b]
Organisation		
Franchise (%)	41.4	34.9[c]
Chain (%)	23.7	23.9[c]
ISO compatible certificate (%)[§]	26.3*	7.8[d]
Separate room for consultations		
Available (%)	97.0	[nd]
Characteristics of room (n = 192)		
Lockable (%)	94.8	[nd]
Accessible for disabled (%)	92.2	[nd]
Only used for consultations (%)	58.9	65.0[e]

[#]Figures obtained by correcting national data for sample data. National data based on:

[a] Unpublished national data from the Foundation for Pharmaceutical Statistics in The Hague on 1,730 community pharmacies and 2,734 community pharmacists in October, 2004

[b] National data on 1,697 community pharmacies and 2,681 community pharmacists per January 1, 2004, which were published by the Foundation for Pharmaceutical Statistics in The Hague in its Annual Report ''SFK Data en feiten 2003''

[c] Unpublished national data from the Public Affairs Department of Royal Dutch Society for the Advancement of Pharmacy on 1,730 community pharmacies in October 2004.

[d] National data on 1,730 community pharmacies in October 2004, which were retrieved from the website of the Foundation for Harmonization of Quality Assessment in the Health Care Sector [http://www.hkz.nl/certificaten.jsp].

[e] Report from Inspectorate for Health Care, based on visits to 196 community pharmacies between November 2002 and January 2003.[19]

*Statistically significant difference ($p < 0.05$) in χ^2-test.

[¶] FTE, full-time equivalent .

[§] Dutch community pharmacies can be certified under the auspices of the Foundation for Harmonisation of Quality Review in Health Care and Welfare (HKZ). The certificate issued by the HKZ is compatible with ISO 9001 [http://www.hkz.nl/]

[nd], not determined

Table 2: Frequency and extent of pharmaceutical consultations in private in Dutch community pharmacies.

Type of consultation	Mean duration of consultation (in min) (range)		Mean number of consultations per month (range)[a]	Mean number of minutes per month spent on consultations (range)	
	Excl. preparation time	Incl. preparation time[b]		Excl. preparation time	Incl. preparation time[b]
Face-to-face	15.9 (4-45)	23.6 (4-105)	8.0 (0-60)	107.4 (0-800)	148.9 (0-1000)
By telephone	7.4 (2-20)	9.2 (2-30)	15.4 (0.3-120)	104.4 (3-700)	127.6 (4-960)
By e-mail	N/A	9.5 (0-30)	1.4 (0-10)	N/A	14.2 (0-200)
Total			24.7	208.7	290.6

[a] Mean number in the 3 months prior to the questionnaire
[b] Preparation time refers to the time that the pharmacist spends before the actual conversation starts (e.g., to check on the pharmacy record, the literature and/or any notes concerning previous contacts with the patient)
N/A: Inquiries were only made on the total time spent on e-mail consultation

Consultations by e-mail are only given by a minority (30.8%) and their mean number is only 1.4 consultations per month. The vast majority of the respondents state that face-to-face consultations are always or regularly given in the pharmacy and only occasionally or never given at the patient's home (93.0 and 89.7%, respectively). Nearly half of the respondents and even a larger part state that face-to-face consultations and telephone consultations always take place immediately without prior appointment (41.5 and 78.4%, respectively). Only a few respondents keep to fixed hours for face-to-face and telephone consultations similar to office hours of general practitioners (5.3 and 1.1%, respectively). Several respondents indicate that they had such fixed hours in the past but discontinued them (13.4 and 3.3% for face-to-face and telephone consultations, respectively), e.g., because there was insufficient interest from patients or because there was a need for consultations on the spot rather than on predetermined hours. Of the respondents providing face-to-face consultations in private, 76.5% draws the attention of patients to this possibility; for telephone and e-mail consultations, this percentage is 47.8 and 83.6%, respectively. Most respondents providing face-to-face consultations (88.9%) draw attention to face-to-face or telephone consultations in personal contacts with patients and/or by way of leaflets; a similar percentage is found for respondents providing telephonic consultations (89.9%). Of the respondents providing consultations by e-mail, 26.0% draws attention to this possibility through the Internet. When questioned about their last personal consultations, the respondents indicate that these consultations were mostly initiated by the patient (74.3, 74.2 and 88.5% for face-to-face, telephone and e-mail consultations, respectively). The initiative was taken by the pharmacy team in 23.0, 16.5 and 1.6% of the cases. The latter occurred more often routinely as the result of a computerised alert (concerning some medication surveillance problem) or the alertness of the pharmacy team than on the basis of any special pharmaceutical care project or protocol.

The major drug classes and topics in the last personal consultations given by the respondents are summarized in Table 3. The drug classes discussed most frequently were the psycholeptics in the face-to-face consultations, the analgesics in the telephone consultations, and the sex hormones in the e-mail consultations. Adverse drug effects and drug interactions/ combinations are ranking first and second, respectively, in the face-to-face and telephone conversations and they occupy the second and third place in the e-mail consultations (these latter rankings should not be considered without reserve, however, because they are based on very low numbers). Other noteworthy details are the first ranking of drug costs in the e-mail consultations and the relatively high ranking of the underlying disease/disorder in the face-to-face conversations (consultations were only classified as such, when they focused on the disease/disorder itself and not on its drug treatment).

Table 3: Absolute and relative frequencies of major drug classes and topics discussed in the last consultations in private given by the respondents.

	Face-to-face	By telephone	By e-mail	National data on prescription volume
Major Drug Classes	(n=245)¶	(n=215) ¶	(n=52) ¶	
N05 Psycholeptics[a]	8.2%	3.3%		10.0%
R03 Drugs for obstructive airway diseases	7.3%	2.8%	1.9%	4.6%
N02 Analgesics[b]	6.1%	9.3%	35.8%	4.2%
N06 Psychoanaleptics[c]	5.7%	2.8%	11.5%	4.5%
A10 Drugs used in diabetes	5.3%	4.7%		3.3%
G03 Sex hormones	3.3%	6.1%	23.1%	3.8%
J01 Antibacterials for systemic use	3.3%	5.1%		4.7%
M01 Anti-inflammatory / antirheumatic products	3.3%	5.1%	1.9%	5.3%
Total	42.4%	39.1%	44.2%	40.4%
Major Topics	(n=258) ¶	(n=218) ¶	(n=67) ¶	
Adverse drug effect	22.5%	19.7%	10.4%)	
Drug interaction/combination	9.7%	8.7%	6.0%	
Underlying disease/disorder	7.8%	2.3%	1.5%	
Drug action/mechanism of action	5.8%	3.7%	4.5%	
Drug choice	4.7%	6.0%	7.5%	
Drug dosage	4.3%	6.4%	0%	
Drug cost/drug substitution	1.9%	3.7%	13.4%	
Total	56.6%	50.5%	43.3%	

¶ Numbers refer to total number of times a specific item was mentioned
a Comprising the antipsychotics, anxiolytics, hypnotics and sedatives
b Including anti-migraine preparations
c Antidepressants, psychostimulants and anti-dementia drugs
d Including gonadotropins, other ovulation stimulants, and anti-androgens

A specific question about the appropriateness of our working definition near the end of our questionnaire was answered affirmatively by 152 of the 198 respondents (76.8%). The respondents who disagreed (n = 45; 22.7%) gave as arguments that they would also like to consider conversations as pharmaceutical consultations, (a) when they take place at the counter; (b) when they deal with certain non-drug issues, such as non-drug aids and devices, and/or (c) when they occur between a patient and a pharmacist's technician[#]. In response to other general statements, almost all respondents agreed that the needs and questions of the patient with respect to care are important (95%), that pharmaceutical consultations are useful (97%) and that they should be given by community pharmacists to distinguish themselves from other suppliers of drugs (95%). Most respondents indicated that neither lack of time (85%) nor lack of a remuneration system (87%) should impede the provision of pharmaceutical consultations but many would welcome a refunding of the cost of pharmaceutical consultations by health insurance companies (78%). Approximately two-thirds of the respondents believed that community pharmacists can provide pharmaceutical consultations on a structural basis (66%), but that they should improve their medical/pharmaceutical skills (68%) and communicative skills (63%) by means of additional education and training. Only 28% of the respondents believed that general practitioners are pleased with the possibility of pharmaceutical consultations between pharmacist and patient. A determinant analysis to assess which factors are significantly associated with the provision of a relatively high frequency of face-to-face consultations per pharmacy (uppermost quartile of pharmacies versus other three quartiles) is presented in Table 4.

There was no significant association with potential indicators of quality (pharmacy ISO certified or affiliated with a franchise) or relative pressure of work (number of registered patients per full-time equivalent pharmacist). There was also no significant association with the pharmacist's views on the need to remunerate consultations in private and the need to improve their medical/pharmaceutical and communicative skills. Conversely, a high frequency of face to face consultations was significantly associated with the absolute number of full-time equivalent pharmacists per pharmacy.

[#]Pharmacy technicians in The Netherlands receive an intermediate vocational training of 2–3 years to qualify. Technician's tasks that are more or less generally recognized are the compounding and dispensing of medicines, the provision of advice on OTC drugs and non-drug health care products, the provision of directions for use and the answering of basic questions about medicines and the underlying disease. More experienced technicians may discuss adherence or medication changes with the patient and perform one-to-one consultations.[23]

Table 4: Determinants of the frequency of face-to-face pharmaceutical consultations in the sample of respondents.

Pharmacy Characteristic	Number of face-to-face consultations per month		Odds ratio (95% CI)	
	≥ 27 (n=51)	< 27 (n=147)	Crude	Adjusted[¶]
Franchise (%)	54.9	36.7	2.1 (1.1,4.0)	1.7 (0.8,3.6)
Chain (%)	17.6	25.9	0.7 (0.3,1.5)	0.9 (0.4,2.2)
ISO compatible certificate (%)	35.3	23.1	0.6 (0.3,1.1)	0.9 (0.4,2.0)
Full-time equivalents of pharmacists (%)				
< 1.1	17.6	41.5	1 (ref.)	1 (ref.)
1.1-2.0	60.8	44.9	3.2 (1.4,7.2)	3.8 (1.4,10.3)
> 2.0	19.6	12.2	3.8 (1.3,10.7)	4.2 (1.1,15.7)
Patient number registered per full-time equivalent of pharmacist (%)				
< 5,500	35.3	27.2	1 (ref.)	1 (ref.)
5,500-8,000	21.6	36.7	0.5 (0.2,1.1)	0.7 (0.3,1.8)
> 8,000	31.4	29.3	0.8 (0.4,1.8)	2.4 (0.8,7.4)
Respondents who agree with the following statement (%)				
Remuneration for pharmaceutical consultations should be introduced	74.5	61.9	1.9 (0.9,3.9)	1.7 (0.8,3.7)
Pharmacists should improve their medical/pharmaceutical skills	68.6	67.3	1.1 (0.5,2.2)	1.1 (0.5,2.6)
Pharmacists should improve their communicative skills	58.8	64.6	0.8 (0.4,1.6)	0.7 (0.3,1.5)

[¶] Adjusted for franchise, chain, ISO compatible certificate, full-time equivalent pharmacists, patient number registered per full-time equivalent pharmacist, and agreement with statements ''Remuneration for pharmaceutical consultations should be introduced'', ''Pharmacists should improve their medical/pharmaceutical skills'' and ''Pharmacists should improve their communicative skills''.

Discussion

Numerous studies on patient education, pharmacist counselling and pharmacist consultations have been conducted in the past, but these concepts often remained ill-defined and may therefore have comprised a range of different activities.[2] For the purpose of our study, we developed a strict definition of pharmaceutical consultations in the community pharmacy that was directly derived from the patient view that the community pharmacist should act more as a personal adviser. This does not imply that we trivialize in any way the importance of contacts between patient and pharmacist's technician, contacts with the pharmacist at the counter, or contacts about non-drugs and devices. It merely reflects that Dutch patients would like to see their community pharmacists to act more as a personal adviser. Over three-quarters of the responding community pharmacists agreed with this approach. Furthermore, most respondents supported the view that they should provide pharmaceutical consultations in private on a structural basis and that they should not be held back by lack of time or remuneration. However, relatively few respondents believed that the general practitioner will be pleased with an increase in pharmaceutical consultations in private. In practice, the respondents provide an average of roughly 1.2 personal consultations per working day. These consultations are

usually not given on fixed hours, and the few respondents who tried this in the past have returned to a more flexible approach. The respondents succeed in giving telephone consultations almost twice as often as face-to-face consultations and in less than half the time needed for a face-to-face conversation. On the other hand, the provision of consultations by e-mail has not yet grown out of its infancy in most pharmacies. As expected, topics concerning medication safety were most prominent in the face-to-face and telephone consultations. However, the underlying disorder (i.e., without direct relation to the medication used for this disorder) was a major subject in almost 8% of the face-to-face conversations, while questions about drug cost/substitution were the most important topic in e-mail contacts. The ability to provide approximately one face-to-face consultation or more per day was only associated with absolute manpower (number of full-time equivalent pharmacists per pharmacy) and not with relative manpower (number of registered patients per full-time equivalent pharmacist). This finding is consistent with a questionnaire study from Northern Ireland, in which the provision of pharmaceutical care by community pharmacists was more extensive, when there was a higher number of pharmacists employed.[17] A plausible but tentative explanation is that various managerial duties in the community pharmacy have to be performed regardless of the pharmacy's size, which puts single pharmacists at the disadvantage of being left with relatively little time for one-to-one consultations. If true, this would make it quite important to reconsider and restructure the way, in which many community pharmacists have currently organized their activities. An investigation that had paid attention to this topic prior to our study was carried out by the Dutch Inspectorate for Health Care. The Inspectorate visited almost 200 community pharmacies between November 2002 and January 2003 to assess several preconditions for the reliable provision of pharmaceutical care. According to this general investigation, ''personal consultations'' were given in nearly every pharmacy in a frequency varying from one consultation per month to 50 consultations per week. Of the pharmacies visited, 65% of the pharmacies had a separate room that was reserved for such ''personal consultations'' and was primarily used for the transfer of information on specific subjects like incontinence, asthma or COPD, and diabetes.[19] Unfortunately, the report of the Inspectorate does not explain what exactly was meant by ''personal consultation'', and it is likely that the Inspectorate interpreted this concept more vaguely than we did in our study. Several limitations of our study should be noted. First, we employed a narrow definition of pharmaceutical consultations, thereby excluding several types of contacts in the community pharmacy considered as pharmaceutical consultations in broader definitions. Almost a quarter of our respondents indicated that they would also like to classify conversations as pharmaceutical consultations, when they occur between a patient and a pharmacist's technician, when they take place at the counter, and/or when

they deal with certain non-drug issues. Our results can therefore not be considered as an indicator of the total extent of pharmaceutical care provided by the responding pharmacists. Our strict definition of pharmaceutical consultation had the advantage, however, that it reduced the risk of different interpretations by different respondents (e.g. on the issue, when a conversation at the counter is still a consultation and when that is no longer the case). A second limitation of our study is that the data were self-reported. Third, the low response rate (25%) may have limited the representativeness of our findings. The responding pharmacies differed from the national picture by being more often certified, so pharmacies with a demonstrable systematic approach to the management of the quality of care were overrepresented in our sample. The significance of this finding is unclear, in particular because being certified did not have a significant effect on the frequency of face-to-face consultations within our study sample (Table 4). Fourth, Dutch pharmacies give relatively much prominence in the dispensing process to pharmacist's technicians, which makes them different from community pharmacies in other countries. However, patients in other countries also have to stand before a counter with little protection of privacy, when they enter a community pharmacy for a prescription or a question. Further research will now have to be carried out to replicate our findings and to analyse in detail the impact of the pharmacist's communication skills[20] and the pharmacist's attitude towards pharmaceutical consultations.[12] It will be even more important, however, to assess patient experiences with pharmaceutical consultations in private and the effects of patient's attitudes.[21]

Conclusions

Our study offers a new perspective on patient-pharmacist contacts, which is directly derived from the patient view that the community pharmacist should act more as a personal adviser. Our findings offer insights into the frequency, nature and determinants of personal pharmaceutical consultations in community pharmacies, such as the modest contribution of e-mail contacts and the significant association between the number of face-to-face consultations in private and the absolute number of full-time equivalent pharmacists per pharmacy.

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CHAPTER 3

Proposal of standardization to assess adherence using medication records – methodology matters

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Abstract

Purpose: Different measures of medication adherence using medication records are currently available. The literature is particularly lacking standardization and operationalization of the assessment methods. In parallel, ambiguous terminology has emerged to describe a deviation from prescribed regimen, forcing the European ABC Project to define three phases of medication use: “Initiation, Implementation, and Discontinuation”. Building up on this taxonomy, we propose a harmonization of standards, as well as definitions of distinct measures and their operationalization to quantify adherence to medication.

Methods: Group discussions and consensus process among all co-authors. Our propositions were generated using our experiences and views in the field of adherence, informed by theory.

Results: We harmonized the concepts of adherence measures within the new taxonomy and propose the standards necessary for the operationalization of adherence measures. Besides a proportion as measure for the extent of implementation of the drug regimen and a time-to value for the persistence with treatment, we propose to add a dichotomous value for the re-initiation of treatment. We listed the methodological issues that should be disclosed in studies on adherence.

Conclusions: We discuss the possible impact of the measures in adherence research. By doing this, we are convinced that results of future adherence research should gain in accuracy. Finally, studies will become more transparent, enabling comparison between studies.

Introduction

Medication records are increasingly collected worldwide and available from prescribing, dispensing or reimbursement databases. They generally contain all necessary elements required to calculate the number of days' supply such as the date of prescribing or dispensing, the quantity dispensed and the prescribed daily dose. Calculations with medication records represent a simple approach to determine how (i.e. adherence) and how long (i.e. persistence) patients are taking prescribed medications. These measures have intuitive appeal, and their value in clinical research has been shown.[1,2] They are objective, non-invasive and economical for use in large populations since they can be easily derived from data routinely collected for administrative or other purposes. The reported calculations of adherence from medication records are indubitably based on the abovementioned elements, but specification of standards for these calculations is missing.[3-5] In the absence of any gold standard, no less than 11 different methods for calculating adherence were identified,[6] the most often used being the MPR (Medication Possession Ratio) and the PDC (Proportion of Days Covered).[7] When applying the 11 different calculation methods to the same set of pharmacy data, Hess et al. obtained adherence rates ranging from 63.5 to 104.8%,[6] demonstrating the dramatic influence of the settings on the computed adherence values. Similarly, 5 different methods for calculating persistence were identified,[3] which resulted in a wide range of values and interpretations when applied to a hypothetical patient. A simulation with reimbursement data of 113,108 patients yielded adherence rates ranging from 15.7% and 97.0%. In fact, of the 47 identified publications, only 4 named all the elements that were included in the calculations. Authors publishing adherence rates mostly omit a description of the operationalization of the assessment methodology,[5] i.e. how the raw data were processed. This lack of transparency regarding the operationalization of adherence measures complicates the comparison of adherence results across studies[6,8,9] and the translation to daily clinical practice.[10]

In parallel and almost inevitably, a proliferation of terms emerged in the literature to describe medication use.[11] They all describe a deviant behaviour and are often used interchangeably, but define different aspects like seeking medical care, acquiring medication or deviating from the prescribed therapeutic plan.[11] As a consequence, an European consortium defined a new taxonomy for the umbrella term "Adherence to medications" which is *"the process by which patients take their medications as prescribed".*[11] It is divided in three quantifiable phases: Initiation, Implementation, and Discontinuation. In this context, we see a need to propose standards and definitions to calculate the adherence measures according to the recently proposed taxonomy.[11]

Aims and objective

Our aims were a) to harmonize the concepts of adherence measures within the new taxonomy; b) to propose the standards necessary for the operationalization of adherence measures; c) to refine adherence calculation with medication data; d) to list the methodological issues that should be disclosed.

Methods

Group discussions among experts in summer 2014, consensus process among all co-authors in November 2014, final consensus on the last version in December 2014. On the basis of recent methodological articles,[11,12] we harmonized the concepts describing medication use behaviour, we set standards for the elements related to the (re)fill of a prescription, and we refined the measures and their basic calculations able of quantifying the three phases of adherence.

Results

Harmonization of concepts and proposed measures describing adherence

The assumptions made for adherence measurements with medication records are listed in Table 1.

Table 1: Assumptions underlying adherence measures with medication records.

Assumptions
Medication records are complete, comprehensive and accurate
The first intake occurred the day of the first prescription or fill
The medication is taken as indicated (e.g., tablet ingested)
Lack of a refill equals a medication is not consumed after the oversupply is exhausted
Medications are not purchased or borrowed from or to another person or venue
No unknown treatment interruptions or dosing changes occurred during the observation period

Initiation is defined as the time from prescription until first dose is taken and is a time-to-event variable.[11] As the exact moment of the first intake is seldom measured, sometimes *Initiation* is defined as the time from prescription until the first medication fill. The output is the number of primary non adherers, i.e. patients with a prescription that is not followed by a dispensing. In studies using solely dispensing databases, the assumption that the day of dispense equals the day of prescription invalidates any quantification for this phase.

Implementation is obtained when the prescribed dosing regimen is compared to the effective patient's dosing history.[11] For this phase, we propose to describe the time spent on and off therapy with several measures.

Discontinuation and *persistence* are driven by the continuity of medication refilling. *Discontinuation* occurs when the next due dose is omitted and no more doses are taken thereafter. Discontinuation is therefore a dichotomous variable. *Persistence* describes the time from initiation until the last dose,[11] i.e. the end of therapy. *Persistence* is therefore a continuous variable. The dimension of time is an integral part of both terms.[4] The maximal permissible length without supply (grace period) can reach from zero (no gaps allowed in medication history) to infinite. Between those two extremes, almost every gap length from 7 to 180 days has been proposed in literature.[13] Setting the cut-off equals to defining the sensitivity of the measure, since the smaller the allowable gap, the higher the number of patients that will be classified as being non persistent.[14]

As patients may restart treatment at any point in time, we propose to introduce the term *Re-initiation* of treatment operationalised as the proportion of patients with a new dispensing after the maximal predefined gap length.

Definition of standards

The definitions of the elements with standards and calculations are summarized in Table 2. We define the *observation period* as the length of the time over which the adherence measures are assessed. The period starts at t_1 at the first (re)fill date, with the assumption that the patient starts medication intake that very day. The period ends either at the last refill date t_n or at an arbitrary date t_a (e.g., a medication review date; t_1 + 360 days). The rationale for such variable end dates is that refills are time-dependent events.

Figure 1 is a graphical representation of the elements defined in Table 2. The observation period runs from the start day (t_1 at the first dispensing date) to the end day (t_n at the last dispensing date, or t_a at an arbitrary date). A: number of days with medication available; B: number of days between two dispensations. Oversupply obtained from A_1 is carried forward to the next possible interval (arrow) at the end of A_3, what is likely to occur in the real world. Oversupply obtained from A_4 is disregarded if t_n is the end date, and added at the end of A_6 if t_a is the end date.

Table 2: Definitions of the elements, with standards and calculations. See Figure 1 for graphical representation.

Element	Definition	Standard and calculation
Start and end points of the observation period	period starts at t_1 and ends at t_n or t_a	t_1 = date of first (re)fill t_n = date of last refill° t_a = arbitrary date°
Observation period	number of days of the entire period°	$t_n - t_1$ or $t_a - t_1$
Quantity dispensed	number of dispensed medication units (e.g., tablets)	[quant_disp]§
Units prescribed daily (UPD)	total dose to be consumed per day according to the dosing instructions	UPD = (nb of units per dose) x (nb of doses per day)§
Number of days' supply (A_n)	number of days with medication available	[quant_disp] / [UPD]
Refill interval (B_n)	number of days between two dispensations	(refill date t_n) - (refill date t_{n-1})
Oversupply	number of medication units accumulated from previous dispensings (stockpile)	If ($A_n > B_n$), then oversupply = ($A_n - B_n$)
Gap	number of days without medication supply	If ($A_n < B_n$), then gap = ($B_n - A_n$)
Maximal gap length	number of days of the longest period of time without supply (after taking carryover of oversupply into consideration).	

° a and n are integral numbers

§ can be an integral or a fractional number

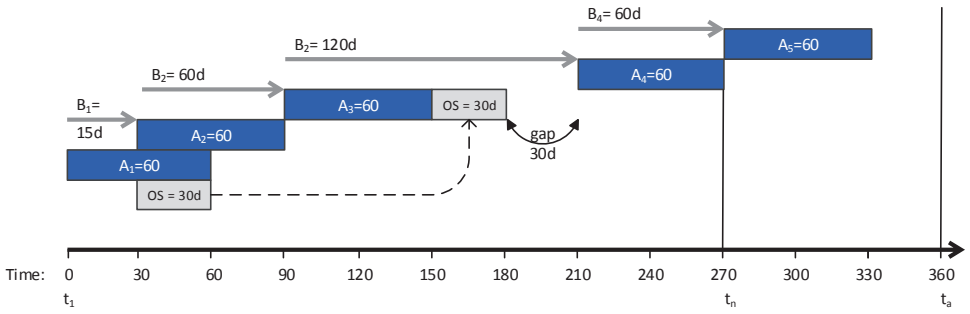

Figure 1: Graphical representation of the elements defined in Table 2.

A=number of days' supply, OS=days oversupply, B=refill interval

We define the *number of days' supply* as the quantity dispensed divided by the units prescribed daily (UPD). The latter equals the amount of medication to be consumed per day, and is calculated with the dosing instruction as (unit(s) per dose) x (dose(s) per day). Changes in dosage regimen according to medical prescription are to be accounted for and exhaustively described. Missing data of the quantity dispensed amounts to exclude this specific data set. In case of missing dosing instruction, extrapolation from the following interval (for t_1) or previous interval (for all other t) is allowed. A data set has to be excluded if dosing instruction is missing for two intervals in a row or if the instruction changed over time and is unknown.

Oversupply (or stockpiling) results from overlapping days' supply of subsequent refill intervals and equals to accumulated medications. Oversupply is allowed with the rationale

that patients get supply before they have exhausted their drug supply, and in a flexible manner according to their daily activities and duties. It is carried forward to the next interval (*carryover*) or at the end of a period with a gap - yet without retroactive compensation - with the rationale that this pattern reflects real life, patients exhausting previous supply before starting the new one. Further, results of a study with hypothetical dispensing patterns suggest that accounting for oversupply in adherence measurement (time-forward approach) performs better than other methods.[8] We do not permit oversupply beyond the observation period, i.e. extra doses beyond the end of the observation period are to be excluded. Oversupply beyond the end date was shown to overestimate adherence measures[6] by blowing up the value of the quantity dispensed.

A *gap* may exist between refills when prior supply is depleted before refill supply is available. It can be (partially) compensated by oversupply from a prior interval. *Hospitalization* or residence in a long term care facility lead to apparent gaps in pharmacy refills and are often interpreted as discontinuation, mostly because they remain unrecognized. If known, we propose to subtract the hospitalization period from the denominator, assuming firstly complete adherence to hospital drugs during hospital stay, secondly that patients don't obtain medications at discharge, and with the rationale that the amount of previous medication at the disposal of the patients after discharge is identical as before hospitalization. To our knowledge, one study observed minimally higher adherence when excluding the number of days the patient was hospitalized from the denominator.[7] If patients use their home medication in the hospital, no adaptation of the calculation is needed.

We define *switching* as one product being initially filled, then a different product in the same therapeutic class being filled at a latter point within the observation period. We define *generic switching* as switching between products with identical ATC code on level 5 (e.g., C03EB01: Lasix 40mg and Furosemide Actavis 40mg). In this case, we consider switch as additive use and carryover is granted under the above mentioned conditions. We define *therapeutic switching* as two different medications, i.e. different ATC code on level 5 (e.g., A02BC01: Omeprazol 40mg and A02BC02: Pantoprazol 40mg; switching within pharmacological group) or on level 4 (e.g., A02BC: proton pump inhibitor and A02BA: H_2-antagonist; switching within the therapeutic group). In this case, we consider switch as continuous use and no overlap is granted, i.e. a possible oversupply of one medication is to be disregarded, with the rationale that a medical reason forced the physician to change medication (e.g., lack of effectiveness, side effects or intolerance). Table 3 lists the mandatory information that adherence studies should disclose.

Table 3: Issues to clearly disclose in adherence studies.

Issues
1. How was the data sample derived? (reimbursement, dispensing, prescribing data)
2. Was there a minimum number of fills and how was the minimum number of (re)fills defined?
3. Were all or only newly treated patients assessed? What was the definition of a newly treated patient?
4. Which adherence phase was assessed? (initiation, implementation, discontinuation)
5. How long was the observation period and how was it defined? (first vs last refill dates or first vs arbitrary end date)
6. How was the prescribed daily dose defined? (instructions for use, assumptions derived from treatment guidelines)
7. Was a single medication or polypharmacy analysed?
8. How were hospitalization periods taken into account?
9. Which was the rationale for the use of threshold (e.g. ≥80% as adherent)?
10. How were missing values handled?
11. How were generic or therapeutic substitution handled?
12. How was dose switching handled?

Refinement of calculation

Time on therapy is best given by the cumulative proportion of time at which medications are available, i.e. in the possession of the patient.

For single medication, we propose the basic algorithm of the MPR (Medication Possession Ratio) that sums the number of days' supply*, divided by the number of days in the observation period, multiplied by 100. Because oversupply beyond the observation period is excluded (see above), the followings are valid:

*If end date is t_n (last refill date), then the numerator is [(sum of days' supply) - (days' supply obtained at t_n)].

**If end date is t_a (arbitrary date), then the numerator is [(sum of days' supply without the last dispensing) + (days' supply obtained at the last dispensing up to the end date of the period t_a).

The MPR ranges from 0 to >100%. For polypharmacy, we propose the basic algorithm of DPPR (Daily Polypharmacy Possession Ratio) that has been described elsewhere.[12] The DPPR does not result from an equation, but from the application of a stepwise algorithm. In brief, the number of all medications available is determined for each day separately over the observation period. A score between 0 (no medication available) and 1 (all medications available) is set. Sum the scores, divide by the number of days in the observation period and multiply by 100 to obtain the proportion of all medications available for daily use. The DPPR ranges from 0 to 100%.

The basic algorithm for oversupply is (number of days' supply A_n) - (days in the refill interval B_n) if $A_n > B_n$ (Figure 1). The basic algorithm for gap is (days in the refill interval B_n) - (number of days' supply A_n) if $A_n < B_n$ (Figure 1). They are calculated simultaneously for each interval and summed up from one interval to the other. Because retroactive

compensation of oversupply is not permitted, supply has always a value ≥0 (negative supply cannot exist).

Time off therapy is best depicted by the days without sufficient medication supply (gaps). The basic algorithm for the time without supply sums the number of days without supply after each interval (after taking oversupply from previous intervals into consideration, Figure 1) divided by the number of days of the observation period, multiplied by 100. Last supply must be excluded. The value ranges from 0 to 100%. Because this value does not capture the dynamics of the time off therapy, we propose further measures. The maximal gap length is the number of days of the longest period of time without supply (after taking carryover of oversupply into consideration). The mean gap value ± standard deviation can be an indicator of dispersion.

Discontinuation and persistence

The maximum permissible period without supply (gap) should be clearly defined. The length of this permissible gap is dependent on the drug(s) studied. In studies with drugs with short half-lives, or when the outcome is linked to a short-term drug effect, a minimal gap length can be justified, where patients are considered non persistent on the first day on which they would have exhausted their drug supply. The clinical relevance of stopping therapy should guide the maximal allowed gap. In most population studies investigating chronic use of drugs for which outcome is linked to long-term drug effects e.g., cardiovascular or antidiabetic medications, a 90-day allowable gap seems adequate to detect true non persistence. A study investigating the impact of several gap selections on persistence observed no major change with increasing gap days >90 days.[15] After setting the allowable gap length, non-persistence is quantified as the percentage of patients exceeding this pre-specified gap.[16]

Re-initiation

The proportion of patients re-initiating therapy is calculated by dividing the number of patients with a dispensing beyond the end of the allowable maximal gap divided by the number of patients defined as having discontinued therapy.

Discussion

We propose standards and their operationalization to quantify adherence to medication within the new taxonomy of the European ABC Group.[11] By doing this, we build on previous consensus based work and link conceptual to operational definitions.

We selected possession-related measures (Medication Possession Ratio (MPR) for single medication, and Daily Possession Polypharmacy Ratio (DPPR) for multiple medication) to

quantify the Implementation phase of adherence, because they are easy to calculate and to interpret (the higher the value, the higher the medication possession). Some researchers have claimed that periods of under- or oversupply of medication may be obscured with possession rates.[13] This might be true as the usual method of calculation used so far does not account for duplication (simultaneous use of multiple agents from the same therapeutic class) and overlapping, the two parameters most frequently responsible for the general overestimation of adherence.[17] The standards that we propose regulate duplication and overlapping and thus, eliminate major elements that distort calculation results. We were also watchful to avoid mathematical equations that would depict impossible situations in real world, like including the supply left over beyond the end of the study period. On the other hand, medication oversupply through early refills (''stockpiling'') is likely to occur in the real world and should be allowed. Our most restrictive standard consists of not allowing retroactive compensation with subsequent oversupply. Our considerations reflect real world situations, since negative supply cannot exist. Patients either have supply (positive value) or they have not (zero value). Consequently, a stepwise algorithm along the intervals instead of an overall equation is needed. This algorithm is clearly more complicated but it identifies periods of time where medication availability was unlikely more precisely.

Defining a cut off value for the number of days without supply (grace period) beyond which treatment is discontinued, i.e. end of therapy, determines non persistence. Part of the challenge is to set a limit that avoids misclassification of patients who restart treatment after a period of discontinuation and would otherwise be lost to calculation if the grace period is too small. As a consequence, we propose to assess "Re-initiation" as a further measure in adherence research. By doing this, the cut off value for discontinuation can still be applied and prolonged gaps between refills - which may not signify cessation of therapy - are still detected. We believe that repetitive "stop-and-go" patterns may have dramatic influence on therapy and have seldom been evaluated properly.[18] Generally, a pharmacologic rationale is lacking for the definition of the allowable grace period or the threshold medication possession ratio. We are aware of one study[19] that defined an allowable interruption gap of 42 days in accordance to a previous clinical trial that reported a potential loss of efficacy of the drug of interest after an interruption of 6 weeks.[20] Thus, different cut-offs must be defined according to the research setting. The search for an universal value set to separate adherence from non-adherence is doomed to failure and can only result in contradictory results.[21]

We excluded from our concepts several terms like "index date" since it has been differently used in literature e.g., as the date of first claim[22] or the first date of the entire period.[7] Further, we excluded the simple measure of refill rates because it is implicit in a

gap-based measure. The number of refills may nevertheless be a valuable calculation for medications that may be used "as needed" without detriment to the clinical condition. It may further be appropriate for medications such as orally inhaled asthma drugs, where information on days' supply may be imprecise.

The way how raw data is obtained (e.g., by pillcount, prescribing, dispensing or administrative data, electronic monitoring of single or multiple medication) determines the content of the database. However, mandatory information for calculations remains drug identification, drug dosage or dosing instructions, quantity of drug dispensed at each (re)fill, and date of each prescription (re)fills. Provided the completeness of the records, the proposed measures can be calculated indiscriminately with prescribing and dispensing databases. In this regard, it is interesting to see that increasingly nationwide personal electronic medicine profiles are stored online for electronic prescribing.[23] However, a recent evaluation of the Danish system showed that it was yet unable to accurately detect non adherence,[23] predominantly because of incorrect dosing information. Experiences from the US after the introduction of the Medicare Improvements for Patients and Providers Act[24] of 2008 showed an increased *use* of e-prescribing in response to an incentive program.[25] One of the most accurate data sources remains the Dutch community pharmacy dispensing system. Of Note: since 1st January 2014 Dutch physicians are obliged to e-prescribing, most of them send the prescription electronically to the pharmacy.

In the future, the measures chosen by a researcher should be determined by the overall goals of the study, i.e. clinical efficacy trials, selection of patients at risk for specific counselling or conditions for reimbursement. Much more, the study population should determine the cut off values. As an example, the length of the observation period may differ if the study population is restricted to new or chronic users of the medications. Finally, because adherence is a complex behaviour with several aspects, it cannot be caught in one number. In any case, a careful description of the definitions and operationalization used is crucial if comparisons between studies are to be made.

Strengths and limitations

Our study has several strengths. First, our standards are close to a real word setting and eliminate overestimation of adherence values. Second, our measures build on the taxonomy established by the European ABC Project and pursue the work of promoting consistency for different experimental investigations. Third, our measures take full advantage of the information available in many databases what most of the current measures of adherence or persistence do not.

We acknowledge some limitations. First, as any indirect method of adherence assessment, our measures are unable to confirm ingestion of the dispensed medication. As a consequence, they function as surrogate measures of medication adherence. However, they can provide an estimate of the highest possible level of medication consumption and thus, can identify those patients not consuming the medication. In that sense, the measures can be considered to have a high specificity. Second, different assumptions are to make, the main being that all medication will be taken at the days' supply indicated. However, a standardization of the assumptions will lead to comparable estimates of adherence across different studies.

By following our propositions, results of future adherence research should gain in accuracy and in confidence, and results between studies should be comparable. We invite researchers to test our standards and to communicate their observations. Ultimately, we soon need generally approved standards and their operationalization, which could be endorsed by an umbrella society, so that health professionals, researchers, health authorities and policy makers can make informed choices for the benefit of patients and society.

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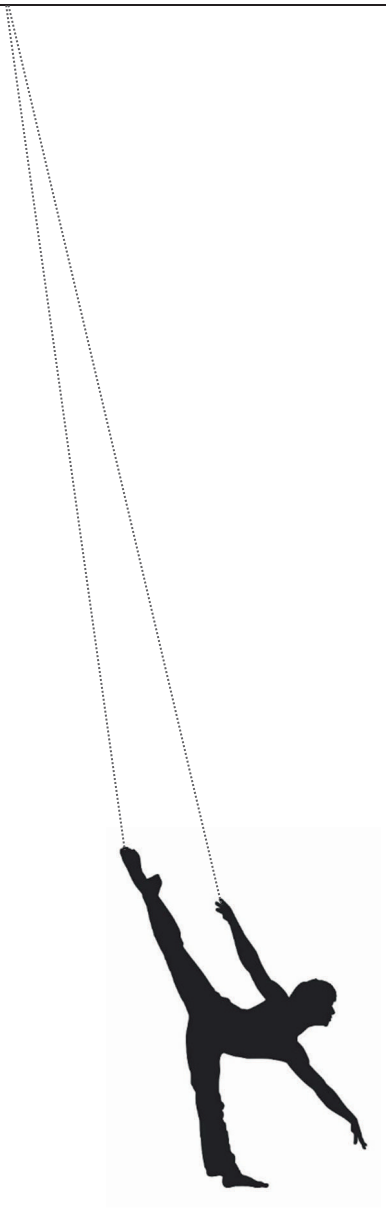
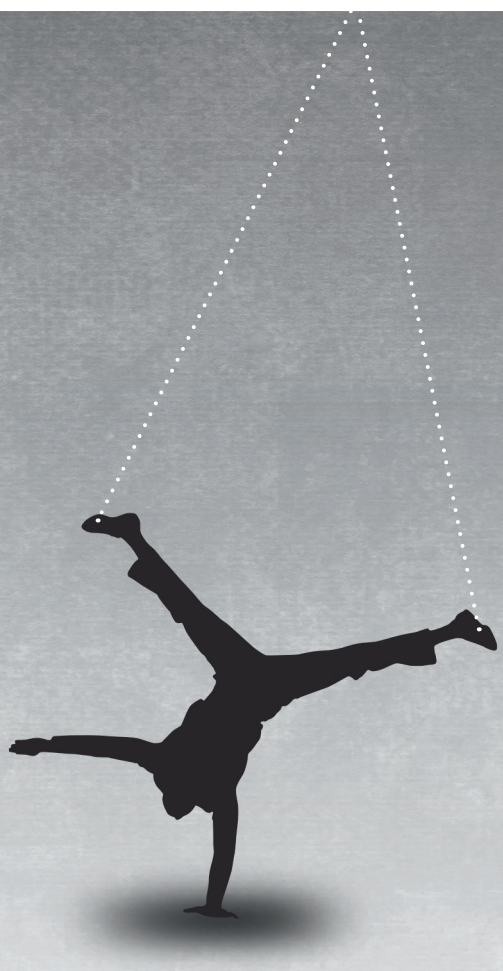


CHAPTER 4

Telephone Counselling Intervention by Pharmacists at the Start of Therapy

CHAPTER 4.1

Effects of a Telephone Counselling Intervention by Pharmacists (TelCIP) on medication adherence, patient beliefs and satisfaction with information for patients starting treatment: study protocol for a cluster randomized controlled trial



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Abstract

Background: Adherence to medication is often low. Pharmacists may improve adherence, but a one-size-fits-all approach will not work: different patients have different needs. Goal of the current study is to assess the effectiveness of a patient-tailored, telephone-based intervention by a pharmacist at the start of pharmacotherapy aimed at improving medication adherence, satisfaction with information and counselling and the beliefs about medicines.

Methods/design: A cluster randomized controlled intervention trial in 30 Dutch pharmacies, randomly assigned to 1 of 2 intervention groups. Each group consists of an intervention arm and a usual care arm. The intervention arm in the first group is the usual care arm in the second group and vice versa. One intervention arm focuses on patients starting with antidepressants or bisphosphonates and the other on antilipaemic drugs or renin angiotensin system (RAS)-inhibitors. The intervention consists of a telephone call by a pharmacist 2 or 3 weeks after a new prescription. A random sample of pharmacies will send questionnaires 3 months after the first prescription. This contains socio-demographic questions, a measure of beliefs about medicines (BMQ), satisfaction with information received (SIMS, abbreviated) and frequency of pharmacy counselling (Consumer Quality Index, CQI, abbreviated). The primary outcome measure will be medication adherence calculated from dispensing records retrieved 12 months after the intervention. Patients' beliefs on medication, perception of the quality of information received and pharmacy counselling are secondary outcomes.

Discussion: The TelCIP study will determine the effectiveness of telephone counselling to improve adherence in patients initiating a new treatment. By measuring satisfaction with information and counselling and beliefs about medication the study will also give clues for the reason of a potential increase in adherence. Finally the study will provide information on which patients are most likely to benefit from this intervention.

Background

Adherence to medication therapy in general is often low.[1-3] Non-adherence to long-term therapies severely compromises the effectiveness of treatment and is therefore critical from both the perspective of quality of life of individual patients and from the perspective of public health and health economics. There are many different factors involved in non-adherence including social and economic factors, the characteristics of the disease and its therapy and health-care provide related factors and patient-related factors such as beliefs about medicines.[3-6] Urquhart et al. and more recently Vrijens et al. argued that three phases of chronic drug treatment can be identified: acceptance of the treatment plan, implementation of the drug regimen and eventually complete discontinuation (non-persistence) of treatment.[7,8] Non-adherence can take place in these three different stages.[8]

Non-adherence cannot be regarded as an isolated problem of the patient. The health care provider has to support patients to improve adherence. Patients need information about their medicines to facilitate their appropriate use and understanding of the benefits and risk.s[5,9,10] Providing patients with appropriate information about medication has been associated with improved adherence resulting in improved treatment outcomes. In contrast, information not addressing patients' needs may produce opposite effects.[11,12] A great part of the information provided by the health care provider is forgotten or remembered incorrectly.[13,14] Therefore it would be desirable to consider repeated opportunities for providing information.[15] But providing information alone is not enough: patients need to be motivated and be involved in decision making.[16] Negative attitudes and barriers that prevent adherent behaviour should be addressed.

Different interventions have been studied to improve adherence. Multidisciplinary and multifactorial interventions were more effective than single focus-interventions. Ideally interventions should focus on practical and perceptual barriers that affect adherence. Practical barriers may include complex dosage regimens, the size of tablets, the cost of prescriptions, the route of delivery (e.g. rectal or oral) and side effects. In contrast, perceptual barriers are more complex and are based on an internal negotiation between the perceived necessity of the treatment and any concerns relating to it. Interpersonal communication provides opportunity to tailor information to the practical and perceptual barriers of a specific patient.[17,18]

Pharmacists can play an important role in improving adherence: they are easily accessible health-care providers, have frequent contacts with patients, have extensive knowledge about drug therapy and are equipped to provide information and monitor patients' experiences and adherence at visit to the pharmacy. However, it is not always possible to tailor counselling to patient needs.[10] Some patients are unable to visit the pharmacy.

Others perceive a lack of privacy in the pharmacy or do not have time for counselling at the moment of the visit. Sometimes patients are already overwhelmed by information provided by other health care providers and therefore not open to receive additional information from the pharmacy.

A different approach might improve patient counselling. Counselling by telephone has proven to be an effective, easy implementable alternative.[19,20] Although it has some disadvantages like the lack of non-verbal communication, it can resolve some of the barriers mentioned above. The patient is counselled in his or her own safe environment and lack of privacy is not an issue. From the health care providers' perspective: it is easier to implement since the calls can be scheduled. Competent employees can be appointed and can better anticipate on the subject.

Given the above we designed an intervention aimed at preventing patients initiating treatment from becoming non-adherent. We will focus on patient starting with lipid modifying agents, Renin-Angiotensin-System (RAS)-inhibitors, antidepressants or bisphosphonates. We choose these medications because (1) they are intended for long-term use, (2) are prescribed frequently enough to enable the inclusion of a sufficient number of patients during the study period, (3) adherence is often low and (4) the characteristics of patients using antidepressants, bisphosphonates or RAS-inhibitors/lipid lowering drugs are different and patients might weigh risks and benefits of these four groups of medicines differently.

The main objective of the study is to assess the effectiveness of a patient-tailored, telephone intervention by a pharmacist at the start of pharmacotherapy on (1) adherence, (2) beliefs about medicines and (3) satisfaction with information and counselling. We also will assess to what extent counselling by telephone fulfils patients' needs.

Methods and design

Study design

We will conduct a multicentre community pharmacy-based, cluster randomized controlled trial (CRT) (Figure 1). Pharmacies are alternately assigned to either group A or group B in a 1:1 ratio. Given the nature of the study design it is impossible for both the researchers and the pharmacists to be blinded to the group assignment. Each group consists of an intervention (TelCIP) arm and a usual care arm. The TelCIP arm in group A focuses on the same medication as the usual care arm in group B and vice versa.

We performed a pilot in three pharmacies in the period of October 2010 to December 2010. In this pilot we tested the manuals, the feasibility, the software to select the patients (queries) and the online registration form. This pilot led to some practical

adjustments in the manuals, the software and the online registration form. The design and the intervention proved to be feasible.

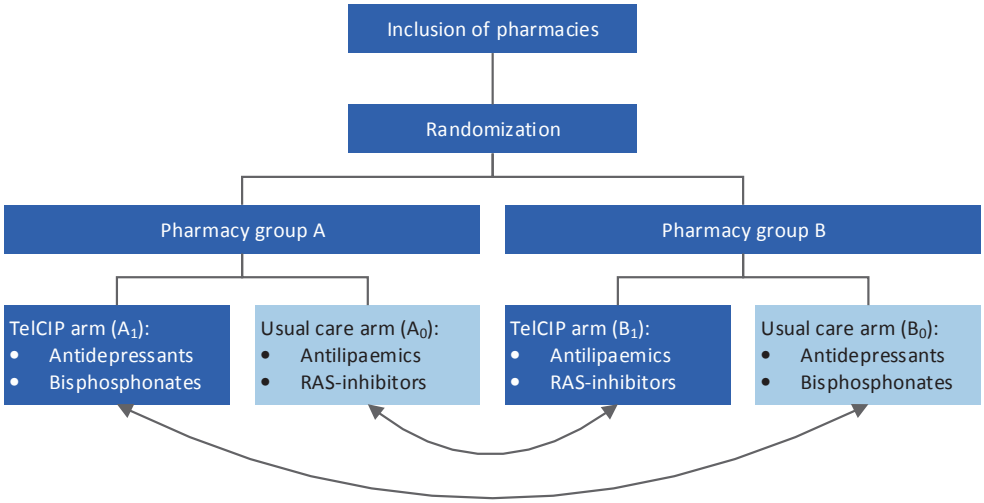

Figure 1: Study design. Pharmacies are randomized in two groups. Each group consists of an intervention (TelCIP) arm and a usual care arm. The TelCIP arm in group A focuses on the same medication as the usual care arm in group B and vice versa.

Recruitment of pharmacies

Independent pharmacies franchisees of 'Service Apotheek' are invited to participate in the study. The study design is presented at 4 regional meetings for pharmacies where they could apply for participation. In a weekly newsletter pharmacies are also invited to participate in the study. The pharmacies are periodically visited by staff of the franchise formula and during these visits; the study is also brought to the attention of the pharmacist. Participating health care providers have to follow an e-learning communication training based on the Health Belief Model. The Health Belief Model (HBM) suggests that adherence behaviour is influenced by perceived severity (beliefs about how severe the condition is), perceived susceptibility (the extent to which the patient feels at risk of suffering from the condition) and the effects and disadvantages of the advised behaviour.[21,22] The course aims to train pharmacists and technicians to understand the opinions and behaviour of patients (related to medication intake). Furthermore the training aims to familiarize pharmacists with the concept of concordance. The course also pays attention to sources for information for patients, possibilities and limitations of package leaflet and the package labels. The course takes about three hours, includes case

studies and a concluding test to assess the level of theoretical knowledge on communication and concordance.

Recruitment of patients

Patients starting with treatment will be recruited from 30 community pharmacies in different areas of The Netherlands in the period between May 2011 and March 2013**.**
Patients in the intervention arm will be selected through an automated selection procedure and presented to the pharmacist. This selection is based on dispensing data and most inclusion and exclusion criteria are incorporated. The same selection will be used to include patients in the usual care group. However not all exclusion criteria can be incorporated in the automated selection and after selection, pharmacist can decide not to include a patient. We will ask the pharmacist to register the reason. However due to the study design the possibility of introducing a selection bias exists, and therefore our primary analysis will be based on the intention to treat principle (ITT). Patients will be included in the analysis if they are eligible according to selection criteria based on the pharmacy data. In a per protocol (PP) analysis we will compare the patients who actually received counselling with patient who received usual care.

Inclusion criteria

Receiving medication for a chronic condition for the first time in 12 months:

- Intervention arm A: starting with an antidepressant or bisphosphonate
- Intervention arm B: starting with a Renin-Angiotensin-System (RAS)-inhibitor or lipid-lowering drug (antilipaemic)

Exclusion criteria

- Under 18 years of age
- Not responsible for their own medication intake
- Receiving their medication weekly in a multidose dispensing system or multi-compartment dispensing system (e.g. Baxter system or 'pill organiser')
- Switching to other medication within the ATC3-group in the 12 months before inclusion
- Receiving medication for a short term indication (e.g. antidepressant for smoking cessation)
- Patients not speaking Dutch nor another language spoken fluently by the health care provider

- Patients starting in the same week with both a medication from intervention arm A (antidepressant or bisphosphonate) and a medication from arm B (RAS-inhibitor or lipid-lowering drug)
- Patients without access to a telephone

Patients in the TelCIP-arms meeting all eligibility criteria receive an information letter, are invited for the study participation and asked for informed consent.

Medication

The definition of the four different classes of medication is described in detail in Appendix 1. We include antidepressants, bisphosphonates, RAS-inhibitors and lipid lowering drugs. Patients switching within a drug class are excluded. For example when a patient switches from an ACE inhibitor to an Angiotensin II antagonist, the patient is not selected.

Ethics

The Medical Ethics Review Committee (METC) of the University Medical Centre Utrecht has considered our research proposal in a meeting 13 July 2010 and concluded that the Dutch Medical Research Involving Human Subjects Act (WMO) was not applicable. Consequently the protocol was submitted to the Institutional Review Board (IRB) of UPPER, Utrecht University and they approved the study protocol. The trial was registered at www.trialregister.nl under the identifier NTR3237.

Usual Care

Usual care in most Dutch pharmacies is as follows: at the presentation of a first prescription for new medication, the pharmacist or technician provides the patients with spoken and written information about the medication and the disease. Instruction protocols are available and can be used. A first prescription is generally provided for a maximum of two weeks. Guidelines recommend that at the first refill, patients are asked about their experiences with the medication. If necessary, additional information or counselling should be provided. Guidelines for counselling at the first refill, however, are not generally implemented.

Intervention

The intervention consists of a counselling call by a pharmacist or a competent technician in addition to usual care. The call is supported by a pre-tested interview protocol. For all medication groups a protocol is developed that describes the specific instructions or side effects for that specific group. For example for antidepressants it is mentioned that it can

take up to 4-6 weeks to notice an effect. In Appendix 1 a translated version is presented. The focus in the protocol lies on both practical and perceptual barriers to take medication. The need for information about the indication, instructions, side effects and treatment plan will be assessed. Also concerns about the treatment, side effects and dependence will be discussed. The pharmacist will also inquire about the experiences with medication intake during the first 2 weeks of treatment (for example if the patient managed to take the medication, or experienced any possible side effect). The call takes place 7 to 21 days after the first prescription. If necessary the pharmacist will provide information, motivate the patient, help the patient to find a strategy to be adherent or refer the patient to the physician. After the telephone call the pharmacist registers all topics that have been discussed in an online database.

Follow up

Dispensing data will be extracted from the pharmacy information system. In The Netherlands all prescriptions are registered in an administrative database, including date of prescription, number of prescribed tablets, prescriber and dosage regimen. A selection of pharmacies will collect data on patient beliefs and satisfaction with information and pharmacy counselling through a written questionnaire. In the selected pharmacies a questionnaire will be sent to patients in both arms, three months after the first prescription. The timeline per patient is shown in Figure 2.

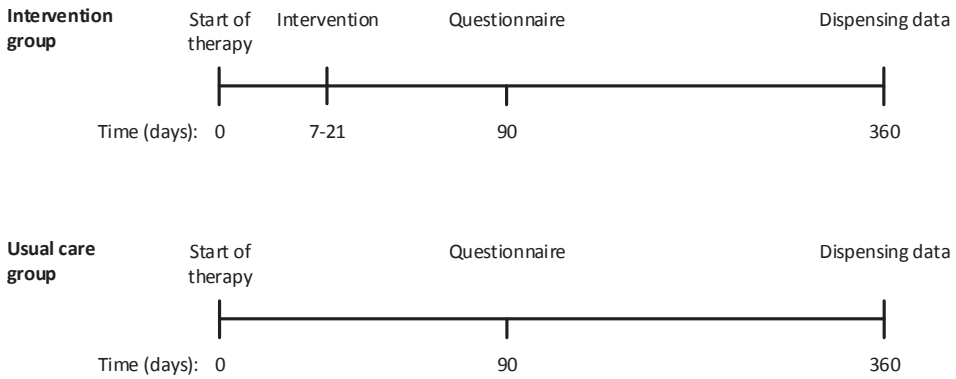

Figure 2: Timeline per patient.

Qualitative analysis of calls

To assess to which extent the pharmacist explores barriers that negatively influence adherence we will record a sample of telephone consultations. These recordings allow a direct analysis of communication without relying on participant reports or simulated

situations.[23] In an amendment the Institutional Review Board of the division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University approved the collection of data. Patients in the intervention arm meeting all eligibility criteria who give informed consent, are asked for permission to record the consultation.

Outcomes

Primary outcome

The primary outcome is the proportion of adherent patients, based on refill adherence. Refill adherence will be calculated as proportion of days covered over the 360 days following the index date by dividing the total days' supply by the number of days of study participation (PDC360).[24]

The index date is the date of the first prescription. The total days supplied will be calculated as the sum of days dispensed within the study period. If a supply exceeds the end of the study participation, this supply will be corrected for exceeding the end of the period. The number of days of study participation is defined as the number of days between the index date and the index date + 360 or the last refill date, whichever comes first. For assessing the last refill date, all refills for any drug will be included. We analyse refill adherence both as a continuous measure and as a dichotomous measure with a threshold of 80%. Patients with a PDC360<80% are defined as non-adherent and patients with a PDC360≥80% are defined as adherent.

Secondary outcomes

Discontinuation

Discontinuation is defined as having a gap of more than 89 days with no medication available within the one year observation period. Cox-proportional hazards will be used to compare discontinuation rates between intervention and control patients.

Beliefs about medicines

Patients' beliefs about medicines will be assessed using the beliefs about medicines questionnaire- specific (BMQs)[25], sent to a random sample of patients three months after the start of therapy. The BMQs assesses both the necessity and concerns regarding prescribed medication. In the questionnaire the name of the specific drug is mentioned in the introduction and wherever it is needed. So for example when a patient starts with simvastatin, one of the BMQ questions will be "I sometimes worry about the long term effects of *simvastatin*". Five items of the questionnaire assesses the beliefs about the necessity and five items assesses the concerns. Each item of the BMQ is scored using a 5-point Likert scale (1= strongly disagree, 2=disagree, 3=uncertain, 4=agree, 5=strongly

agree) therefore the individual score ranges from 5 to 25. The results will be expressed as the score on both domains and as the necessity-concerns differential which is the difference between the score on the necessity scale and the concern scale. The results will also be expressed using the two separate scales, divided at the median to generate four attitudinal groups: accepting (high necessity, low concerns), ambivalent (high necessity, high concerns), sceptical (low necessity, high concerns) and indifferent (low necessity, low concerns).[26-28]

Satisfaction with information

The satisfaction with information provided by health care providers like pharmacists can be assessed with the satisfaction with information about medicines scale (SIMS). As with the BMQ, the name of the specific drug was mentioned in the questionnaire. We used 9 of the 17 items of the original questionnaire.[29] Each item refers to a particular aspect of medicine use. Not all items are used; firstly because some items are not relevant for all four groups of medication, for example “Whether the medication will make you feel drowsy” and “Whether the medication will affect your sex life”. Asking patients these questions when they are not relevant can increase the concerns and thereby influence adherence. Secondly our goal is not to assess the satisfaction in general, but to study the effect of the intervention on satisfaction with information. Thirdly we want to reduce the total number of questions in the questionnaire. We use the items as mentioned in Table 1. We are interested in the effect of the intervention on specific subjects of information and not in an overall satisfaction score. Validation of the combination of the items is therefore not relevant to our study.

Patients are asked to rate the amount of the information received as follows: “too much”, “about right”, “too little”, “none received” and “none needed”. To assess a total satisfaction rating, for each item a score is calculated: if the patient is satisfied (answered “about right”) a score of 1 is given. When the patient is not satisfied (answered “too much”, “too little”, “none needed” or “none received”) this is scored 0. So scores range from 0 to 9, with a high score indicating a high degree of satisfaction. We will calculate a satisfaction score on the same way but based on patients who answered “none received” and “none needed”.

Table 1: Presentation of selected SIMS items.

Item number	SIMS item	Original number
1	How long it will take to act	5
2	How you can tell if it is working	6
3	How long you will need to be on your medicine	7
4	How to get a further supply	9
5	Whether the medicine has any unwanted effects (side effects)	10
6	What are the risks of you getting side effects	11
7	What you should do if you experience unwanted side effects	12
8	Whether the medicine interferes with other medicines	14
9	What you should do if you forget to take a dose	17
Excluded items:		
	What your medicine is called	1
	What your medicine is for	2
	What it does	3
	How it work	4
	How to use your medicine	8
	Whether you can drink alcohol whilst taking this medicine	13
	Whether the medication will make you feel drowsy	15
	Whether the medication will affect your sex life	16

Patient's experience with counselling

The questionnaire contains 4 items adapted from the consumer quality index (CQI) pharmaceutical care[30,31]. In these items the overall experience of different aspects of counselling related to the new medication, is assessed (see Table 2). In the original CQI the patient can answer on a 4-point Likert scale ("never", "sometimes", "often", and "always"). But since we are only interested in the counselling in the first three months since the start of therapy, patients are offered to indicate "yes", "no" or "I don't remember". Patients reporting they received counselling (answered "yes") will be scored 1 and patients answering "no" or "I don't remember" will be scored 0. The total score ranges from 0 to 4.

Table 2: Frequency of aspects of counselling (adapted from Consumer Quality Index).

Item number	Question
1	Did a pharmacist or pharmacy-employee ask you about your experiences with the medication?
2	Did a pharmacist or pharmacy-employee ask you if you suffered from any side effects?
3	Did a pharmacist or pharmacy-employee provide enough personal counselling?
4	Did a pharmacist or pharmacy-employee ask you if you manage to take your medication as prescribed?

Other outcomes

All telephone calls and attempts are registered in a database to monitor the implementation in daily practice. For every call or attempt different aspects are registered:

- Date and duration of the call, number of attempts, age and gender of patient, reasons for not calling the patient
- Early discontinuation: did the patient start with the medication or did he/she decide not to start?
- Different aspects of knowledge are assessed by the pharmacist on a 5-point scale "Good", "Sufficient", "Poor", "Bad", "Not discussed"
- Experiences and attitude towards medication are assessed by the pharmacist
- Advices given during consultation
- Contact with prescribing physician in response to consultation

Sample Size

Power calculation is focused on the primary outcome, the proportion of adherent patients. With a type one error (α) for a two sided test of 0.05 and a probability of rejecting the null hypothesis of 0.80 (1-β) 294 patients per arm are needed for demonstrating an improvement of the proportion of adherent patients from 70% to 80%.[32] For cluster randomization a correction is needed based on the Intraclass correlation coefficient (ICC). When using ICC=0.02 we need at least 15 pharmacies to include at least 30 patients per group of medication for the intervention (4), so 15*30*4=1800 patients in the intervention arms and 1800 in the usual care arms. We expect an average response rate of 30% on the questionnaires and with the aim to receive at least 100 responses per arm, we estimated to invite at least 670 patients to participate in the survey.

Statistical analysis

The primary analysis is based on the intention to treat (ITT) principle e.g. in the intervention group all patients who should have received the intervention will be included. Patient characteristics between groups will be compared using Student's t-test or χ^2-test. Because it is likely that the PDC360 will not be normally distributed, PDC360 differences between groups will be compared using the nonparametric Mann-Whitney U test. We use logistic multilevel analysis to study the effect on the dichotomous primary outcome (adherent yes or no). The outcome of complete discontinuation will be assessed using Cox-proportional hazards. We consider a p-value of less than 0.05 to be statistical significant. In a second analysis effect modification and confounding will be assessed. Effect modification is defined as a significant interaction ($p<0.10$) between group allocation and the variable in question. In a per protocol (PP) analysis we include in the intervention group only patients who actually received the call.

Handling and storage of data and documents

All patient data will provided to the Utrecht University by the participating pharmacies according to a procedure to protect the subjects' privacy. Data with regard to the patients' identity were coded anonymous by the participating pharmacies.

Discussion

This is the first large intervention trial in The Netherlands to study the effect of telephone counselling by pharmacists on adherence. Although pharmacist can play an important role in improving adherence, in daily practice not all patients receive optimal care. The studied intervention is a way to deliver patient-centred care. And can be a solution to barriers in daily practice and that therefore more patients receive appropriate care. We also recognize that this intervention might not be appropriate for every individual patient, by including sufficient patients in 4 medication groups we expect to gain insight into which patients benefit most of this intervention.

The quality of the intervention depends on the competences and skills of the pharmacist. We try to assure treatment integrity by providing an interview protocol, an obligatory communication training and the obligation to document every counselling-call in an online database. Although it is likely that there will remain some differences between pharmacists, our goal is not to study the effect of an intervention in an ideal, perfectly controlled situation, but to study it in daily practice. We believe that this increases the external validity since it reflects current practice. The qualitative analysis of (a sample of) the telephone calls, will provide more insight in the intervention as provided by different pharmacists.

The intervention focusses on patient starting treatment and the aim of the intervention is to assess both practical and perceptual barriers that can influence adherent behaviour. These barriers can both be intentional or non-intentional and especially at the start of therapy it can be a mix of both. Moreover a recent study suggests that unintentional non-adherence is influenced by medication beliefs, chronic disease and socio-demographics.[33] So before a health care provider can tailor the intervention to intentional or non-intentional non-adherent behaviour, the barriers should first be assessed.

Assessment of adherence will be based on pharmacy data. Studies show that this is a valid method. In the Netherlands most prescriptions are filled for three months, irrespective of the frequency of dosing. Therefore, we expect to find enough contrast to assess the effect of the intervention on refill adherence.

We will conduct this study in different pharmacies in different regions of The Netherlands which will improve the external validity and will make it possible to perform an inter-pharmacy comparison.

Limitations

The cluster randomized design of the study may compromises the internal validity of the study since difference at baseline between the levels of the provided care between pharmacies cannot be ruled out. It is likely that a part of the patients in the intervention groups will not be available for the intervention, because contact details are lacking or patients cannot be reached. Since in the control group these patients cannot be excluded this can cause a selection bias in the per protocol analysis.

Conclusion

Upon completion of this study will have knowledge if and for which group of high-risk patients, counselling by telephone at the start of a pharmacotherapy is (most) effective in improving adherence. Also will be clear how the intervention affects patients' perceptions on medication and pharmaceutical care.

List of abbreviations

ATC: Anatomical Therapeutic Chemical
BMQ: Beliefs about Medicines Questionnaire
CQI: Consumer Quality Index
HBM: The Health Belief Model
ICC: Intraclass Correlation Coefficient
ITT: Intention To Treat
PDC360: Proportion of Cays Covered of 360 days period
PP: Per Protocol
SIMS: Satisfaction with Information about Medicines Scale
RAS: Renin-Angiotensin-System

Competing interests

The authors of this protocol disclose no financial conflict of interest pertinent to this study.

Authors contributions

MK wrote the first draft of the manuscript. MK, MB, KG and RH participated in the design of the trial and study methodology and review of the manuscript. KG, LD, MB and RH made critical revisions to the manuscript. All authors read and approved the final manuscript.

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Appendix 1: list of included medication

Table 3: Name and ATC-code of the included medication.

RAS-inhibitors	
ATC-code	Name
C09AA01	captopril
C09AA02	enalapril
C09AA03	lisinopril
C09AA04	perindopril
C09AA05	ramipril
C09AA06	quinapril
C09AA07	benazepril
C09AA08	cilazapril
C09AA09	fosinopril
C09AA10	trandolapril
C09AA15	zofenopril
C09BA01	captopril and diuretics
C09BA02	enalapril and diuretics
C09BA03	lisinopril and diuretics
C09BA04	perindopril and diuretics
C09BA05	ramipril and diuretics
C09BA06	quinapril and diuretics
C09BA09	fosinoril and diuretics
C09BB02	enalapril and lercanidipine
C09BB04	perindopril and amlodipine
C09BB10	trandolapril and verapamil
C09CA01	losartan
C09CA02	eprosartan
C09CA03	valsartan
C09CA04	irbesartan
C09CA06	candesartan
C09CA07	telmisartan
C09CA08	olmesartan
C09DA01	losartan and diuretics
C09DA02	eprosartan and diuretics
C09DA03	valsartan and diuretics
C09DA04	irbesartan and diuretics
C09DA06	candesartan and diuretics
C09DA07	telmisartan and diuretics
C09DA08	olmesartan medoxomil and diuretics
C09DB01	valsartan and amlodipine
C09DB02	olmesartan medoxomil and amlodipine
C09DX01	valsartan, amlodipine and hydrochlorothiazide
C09DX03	olmesartan medoxomil, amlodipine and hctz
C09XA02	aliskiren
C09XA52	aliskiren and hydrochlorothiazide

Lipid lowering drugs	
ATC-code	Name
C10AA01	simvastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin
C10AA07	rosuvastatin
C10AB02	bezafibrate
C10AB04	gemfibrozil
C10AB08	ciprofibrate
C10AC01	colestyramine
C10AC02	colestipol
C10AC04	colesevelam
C10AD02	nicotinic acid
C10AD06	acipimox
C10AX06	omega-3-triglycerides incl. other esters and acids
C10AX09	ezetimibe
C10BA02	simvastatin and ezetimibe

Bisphosphonates	
ATC-code	Name
M05BA01	etidronic acid
M05BA02	clodronic acid
M05BA03	pamidronic acid
M05BA04	alendronic acid
M05BA06	ibandronic acid
M05BA07	risedronic acid
M05BB01	etidronic acid and calcium, sequential
M05BB02	risedronic acid and calcium, sequential
M05BB03	alendronic acid and colecalciferol
M05BB05	alendronic acid, calcium , colecalciferol, sequential

Antidepressants	
ATC-code	Name
N06AB03	fluoxetine
N06AB04	citalopram
N06AB05	paroxetine
N06AB06	sertraline
N06AB08	fluvoxamine
N06AB10	escitalopram
N06AX05	trazodone
N06AX11	mirtazapine
N06AX16	venlafaxine

Appendix 2: Generic interview protocol

Space for a label with the address of the patient

Call attempt	Date:	Start time:	End time:	Employee
1				
2				
3				

Patient number: _____

Introduction

Good afternoon Madam/Sir, you speak with [name] of [name of pharmacy]. Around [date] you received from us for the first time [name medicine]. As an extra service we call clients, who recently started with a medicine, to inquire about your experience with the use of the medicine. Do you have some time?

- ❑ No → "Can I call you at another moment?"
  - ❑ Yes. Note date and preferred time on the protocol
  - ❑ No. "May I ask why not?"…. "Thank you for your time. If you have any questions, you can always call me or visit the pharmacy".
    Record the reason on the website
- ❑ Yes, I have some time at this moment
  - ❑ → Explain the (goal) of the study and ask for informed consent.
    Does the patient consent? If yes, then continue with the protocol. If no:" *Thank you for your time. If you have any questions, you can always call me or visit the pharmacy".*

Directions for the call:

1. *What's the reason that the physician prescribed this drug?*
   Objective: strike up a conversation with someone with a relative simply question. Identify whether the indication/reason for prescribing is known.

	Good	Sufficient	Moderate	Poor	Not discussed
Knowledge of indication/reason	❑	❑	❑	❑	❑

2. *Have you started with [name medicine]?*
   If the patient has not started: identify the reason. Pay attention to resistance to the use of medications specifically and in general.
   If the patient has stopped: ask the reason:_____

3. *What is your experience so far? How is it going?*
   Objective: identify experiences, motivation and attitude. Pay attention to the motivation. Pay also attention to "doubt in the voice". Try to discover whether there are any obstacles for not using the medicine. Ask more if something is not clear. Don't try to come directly with solutions and answers. Let the patient formulate the objective of the therapy. Pay attention not only to side effects, but also practical issues such as breaking tablets.

4. *What has already been told about this medicine?*
Objective: to get a general impression of patients' knowledge. Pay attention to the next aspect: directly asking the knowledge of the patient can be seen as an exam. When you suspect a gap in one's knowledge or incorrect knowledge: *What do you want to know about this medicine? Shall I tell you something about […gap…]?* If you give some explanation ask if it is sufficient and/or if there are more questions.

Background information:
Statins (cholesterol synthesis inhibitors) inhibits the production of cholesterol in the liver and reduce the amount of cholesterol- and fat in the blood. **Ezetimibe** inhibits the absorption of cholesterol in the body. Use the medicine continuously. The effect of the **statins** reaches the maximum after 4-6 weeks
RAS-inhibitors lower blood pressure and improve the output of the heart. Use the medicine continuously. The effect of the **RAS-inhibitors** reaches the maximum after 3-6 weeks
Bisphosphonates bind to calcium in the bones and inhibit the demolition of the bone. By combining it with sufficient calcium and vitamin D, your bones become stronger. You will not notice the effect of the medicine. But the risk of bone fractures will become smaller. Physicians prescribe this for treatment of bone loss or to prevent it. Use the medicine continuously.
SSRI's, mirtazapine, venlafaxine help to bring balance to some important substances in the brains. They work best in combination with a physician or psychiatrist. The medication improves the complaints, but cannot take away the cause. Use the medicine continuously. Mostly they start working after 2-4 weeks. For elderly sometimes even after 6 weeks.

For more information about the side effects: see below:

Knowledge about:	Good	Sufficient	Moderate	Poor	Not discussed
mechanism of action/effects	❑	❑	❑	❑	❑
the onset of action	❑	❑	❑	❑	❑
the side effects	❑	❑	❑	❑	❑

5. *What do you think of getting this medicine? What's your view?*
Objective: assess motivation and attitude, needs and concerns. What is for the patient the objective to use the medicine?
Alternative formulations: *Do you think that it is important to use this medicine? Are you worried about the side effects in the long term?*

Answer the following statements as a result of the conversation:	Totally agree	Agree	Agree/ disagree	Disagree	Totally disagree	Not discussed
The patient has doubts about the necessity of treatment	❑	❑	❑	❑	❑	❑
Patient worries about side effects	❑	❑	❑	❑	❑	❑
Patient worries about dependence	❑	❑	❑	❑	❑	❑

6. *How long will you have to use the medicine?*
   Objective: is it clear how long the patient has to use the medicine?
   Pay attention to the next aspect: try to identify if there is some possible resistance present. *"What's your view on it?"*
   If necessary: tell the patients that they always can contact the doctor or pharmacist.

7. *Do you know how you can get a refill?*

8. *Are you suffering from any side-effects caused by the medicine?*
   Objective: identify if the patient experienced side effects. If someone doesn't have side effects: if necessary continue with asking if it is clear which side effects can appear. Do this to prevent that a side effect will not be recognized.
   Additional information:
   Side effect **statins**: muscle pain, joint pain, muscle weakness, muscle cramping. Gastrointestinal complaints, especially in the beginning. If you use the medicine with food, then you can prevent this.
   Bisphosphonates:
   Sometimes: irritated oesophagus. Take medication with full glass of water (no milk) while standing up or sitting up right. After intake, stay 30 minutes up right to prevent that the tablet sticks to the oesophagus. If you get any pain behind the sternum (chest), contact your physician.
   Rare: gastro-intestinal problems, headache, joint pain
   Very rare: loss of hair, reduction of vision, pain in jaw, pain in groin, thigh or hip.
   SSRI's: most of the time side effects like gastro-intestinal problems, headache, reduced libido, agitation (nervous feeling, distress, confusion) or trembling will fade within 1-2 weeks.
   Mirtazapine and venlafaxine:
   More than 10% of the patients: headache, dry mouth, nausea and sweating. 1-10%: vomiting, diarrhoea, lethargy, fatigue, dizziness, trembling, strange dreams, distress, insomnia, muscle ache, joint ache, back ache, orthostatic hypotension and exanthema.

	Totally agree	Agree	Agree/ disagree	Disagree	Totally disagree	Not discussed
Patient experienced side effects	❑	❑	❑	❑	❑	❑

9. *How often do you use the medicines?*
   Objective: Try to find out if the patient has problems to use the medicine daily/weekly.
   Please prevent to be judgmental. Support the patient in self-proposing solutions.
   Continue with asking: *"Are you able to use the tablet …time(s) a day/week?"*
   Forgotten? **Statins/RAS-inhibitors**: If there are more than eight hours left before taking the next medicine and you use the medicine only once a day, then you can better use the medicine. If there are less than eight hours left, then you can skip it.

10. *When (at what time/moment) do you use the tablets?*
    Background: see prescription label. Details:
    Statins: Atorvastatin, rosuvastatin, ezetemib: every moment of the day. Other statins: in the evening. In the evening is the production of cholesterol by the liver the highest. At this way you have the most benefit.
    Fluvoxamine: preferably 1 dose in the evening. For adults using more than 150mg per day, divide it in to 2-3 gifts per day. For children and adolescents using more than 50mg per day, divide it in to 2 gifts. If different doses per day, take the highest before going to sleep.
    Mirtazapine: preferably 1 dose in the evening or when 2 doses are needed: take one in the morning and one in the evening and take the highest dose in the evening
    Paroxetine: preferably in the morning
    Bisphosphonates: Take the tablet in the morning, directly after getting up. After half an hour you can take your breakfast. This will reduce the effect of food on the absorption.

	Good	Sufficient	Moderate	Poor	Not discussed
Knowledge about time to use medication	❑	❑	❑	❑	❑

11. *What are your expectations concerning the use of your medication?*
    Are there any obstacles for you? How can I help you with this? You can think to help for example with a compliance card, schedule when to use a medicine or week delivery.

Rounding up the counselling call:

- ❑ Repeat agreements. Summarize.
  - ❑ Do you have more questions?
  - ❑ Can I sent you a quarterly a newsletter about [name subject]? **Write the answer on the survey.**
  - ❑ This pharmacy is working on a study by the University Utrecht on information provided by the pharmacy. Can we send you a postal questionnaire approximately 3 months from now? **Write the answer on this protocol**

Thank you for your time. If you have any questions, you can call the pharmacy or visit the pharmacy.

Register the counselling in the online self-report

Additional questions about the consultation

12. It is possible that the patient has made, with or without a consultation with the doctor, changes in the use of the medication. Can you specify whether the following changes have been made:

	Yes	No	Unknown
In consultation with a doctor, the drug is replaced by another drug.	❑	❑	❑
In consultation with the doctor, the patient has stopped the therapy and there is no alternative start.	❑	❑	❑
Without consulting the doctor, the patient discontinued with the therapy.	❑	❑	❑
The patient has changed the daily use without a consultation.	❑	❑	❑

13. What advice have you given *during* the consultation? (Multiple answers possible)
    - ❑ Advice related to the intake of the medicine
    - ❑ Explanation of the duration of the therapy
    - ❑ Explanation/motivation to the indication
    - ❑ Explanation of possible side effects
    - ❑ Explanation possible dependence
    - ❑ Other, _____

14. Which intervention is in response to the consultation? (Multiple answers possible)
    - ❑ Pill timer provided
    - ❑ Drug intake schedule provide
    - ❑ Sign up for chronic medication service
    - ❑ Sign up for weekly dose system
    - ❑ Other, _____

CHAPTER 4.2

This is your pharmacist calling: are you happy with your new medication? Results of a treatment fidelity study

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Abstract

Background: Guidelines recommend counselling by pharmacists at the start of medication therapy. In the Telephone Counselling Intervention by Pharmacists (TelCIP) trial we studied the effects of telephone counselling on medication adherence. In order to interpret the effects of a multi-centre behavioural intervention, it is necessary to enhance the likelihood of consistent implementation and to monitor the actual execution of the intervention (treatment fidelity). To improve treatment fidelity, activities and strategies on different domains can be used, both in the design of the study and in the delivery of the intervention.

Objective: The aim of this study was to assess treatment fidelity of a Telephone Counselling intervention by Pharmacist (TelCIP).

Setting: 51 community pharmacies in the Netherlands.

Method: The Behaviour Change Consortium (BCC) treatment fidelity framework of the National Institute of Health was used to assess treatment fidelity. The framework addresses strategies on five domains. The presence and implementation of these strategies in the TelCIP trial was assessed using the trial protocol, pharmacy dispensing data and providers' self-reports.

Main outcome measure: Treatment fidelity on five domains: 1) study design, 2) provider training, 3) delivery of treatment (intervention), 4) receipt of treatment and 5) enactment of treatment skills.

Results: Treatment fidelity was high for the study design as most of the suggested strategies in the BCC framework were implemented. No characteristics were described a priori with regard to provider training and skill acquisition was not assessed. Fidelity on delivery of the intervention was high as most delivery strategies mentioned in the framework were implemented, e.g.in 80% of the calls all knowledge items from the interview protocol were discussed. There was evidence of fidelity on receipt of treatment but enactment of treatment skills was not assessed.

Conclusion: Overall, evidence was found for sufficient treatment fidelity of the TelCIP trial. Moreover this study demonstrates the use and value of the framework to assess treatment fidelity. It also stresses the relevance for researchers to consider treatment fidelity when designing and evaluating a trial.

Introduction

Guidelines recommend pharmacists to provide patients with information about the benefits and risks and the correct use of medication.[1-3] As such, pharmacists are expected to promote medication adherence from the start of a therapy onwards.[4,5] Factors hampering counselling at the start of therapy could be overcome by providing pro-active counselling by telephone.[6] To improve counselling at the start of therapy the Telephone Counselling Intervention by Pharmacists (TelCIP) study was designed. Primary goal of this intervention was to increase medication adherence. While generally much attention is paid to outcomes of interventions, less is known about how these interventions are implemented during the trial. Conclusive statements about the effect of a behavioural intervention cannot reliably be made without attention for treatment fidelity.[7,8]

Treatment fidelity can be defined as the permanent monitoring and enhancement of the accuracy and consistency of an intervention to ensure it is implemented as planned and that each component is delivered in a comparable manner to all study participants.[8,9] Attention for treatment fidelity is both important during the design and during the implementation phase of a trial. Imagine a trial demonstrating positive outcomes of an intervention. Without information on treatment fidelity, the study results can be due to an effective treatment or to unknown factors that may have been unintentionally added to or omitted from the treatment (type I error).[8] On the other hand when the study has no effect, this can be either due to ineffective treatment or lack of treatment fidelity (type II error). The Treatment Fidelity Workgroup of the National Institutes of Health (NIH) Behaviour Change Consortium (BCC) developed a treatment fidelity framework[8,9] and suggests implementing strategies and activities on all domains to ensure that the intervention is implemented as planned.

Aim of the study

The aim of this study was to assess treatment fidelity of the Telephone Counselling intervention by Pharmacists.

Method

Study design, setting and population

This fidelity study is part of the cluster randomized TelCIP trial of which the trial protocol has been published elsewhere.[10] The main aspects of the study will be explained briefly. Pharmacies were recruited in two phases. In phase I, independent pharmacies were invited and in phase II, pharmacies with a pharmacist trainee (BPharm) participated.

Patients were recruited between March 2011 and March 2013. Patients ≥ 18 years who filled a first prescription in 12 months for an antidepressant, bisphosphonate, RAS-inhibitors or statin were identified by an automated search in the pharmacy information system that was performed on a weekly basis. Patients were excluded if they were not responsible for managing their own medication or if the medication was prescribed for a short-term indication such as smoking cessation.

51 pharmacies were assigned to one of two arms. Arm A provided the intervention for patients starting with antidepressants or bisphosphonates and arm B for RAS-inhibitors and statins. Within every pharmacy the pharmacist assigned a staff member responsible for performing the intervention. This could be the pharmacist (PharmD) or a non-pharmacist with a bachelor degree, pharmacist trainee or pharmacy technician. In this paper we use the term pharmacist referring to the participating health care provider irrespective of the educational level, unless stated otherwise. The term pharmacy practitioner (PP) is used to refer to non-pharmacist with a bachelor degree, including pharmacist trainees. In total 1800 patients had to be included: 30 patients per medication class in the first phase and 5 patients/medication class in the second phase. Pharmacies in the first phase received a financial incentive from a health insurance company, but only when a 'remuneration goal' was reached.

The assigned staff member received a training based on the Health Belief Model (HBM), which took three hours. The HBM suggests that adherent behaviour is influenced by perceived severity of the disease and the perceived effects and disadvantages of the advised behaviour.[11-13]

Patients in the intervention arm received a phone call 7-21 days after the start. Goal of this call was to assess barriers that hamper adherence. Pharmacies received a medication class specific interview protocol (see Appendix 2 of the trial protocol for the generic version).

The pharmacists had to complete an online self-report for every selected patient (see Appendix 1). This self-report contained sections about 1) patient characteristics, 2) type of staff member that called the patient 3) characteristics of the phone call (e.g. length), 4) patient self-reported adherence, 5) patient knowledge and reported barriers, and 6) additional interventions and information provided. The pharmacist had to rate the knowledge items from the protocol per patient and could choose answers ranging from 'good', 'sufficient', 'moderate' to 'bad' plus the option 'not discussed'. Statements on patient's barriers and experience of side effects were rated on a 5-point Likert scale (from 'totally agree' to 'totally disagree') plus the option 'not discussed'. Also frequency and nature of given advice or treatment recommendations, changes in treatment and attributive interventions (like providing a memory aid) had to be registered. Pharmacies

coded patient data to protect patients' privacy. The study protocol was approved by the institutional review board from the division of Pharmacoepidemiology and Clinical Pharmacology at Utrecht University. The trial was registered at the Dutch trial registry via www.trialregister.nl under the identifier NTR3237.

Treatment fidelity framework and analysis

The BCC treatment fidelity framework[9] addresses five domains: 1) study design, 2) training health care providers, 3) delivery of intervention, 4) receipt of intervention, and 5) enactment of intervention skills.[8,9] On all domains strategies have been suggested by Borrelli et al. to increase fidelity.[9] The BCC framework[9] was used for the assessment of implementation of these activities/strategies in design and implementation of the TelCIP trial. Four data sources were used for the assessment: the published trial protocol, the study manual, dispensing data and data of self-reports filled out by the pharmacist.

Possibilities of selection bias were studied by linking dispensing data and self-reports to compare characteristics of non-registered patients with registered patients and with patients who received the intervention. Characteristics studied included age, gender, chronic disease score (CDS) and social status score. The CDS uses medication dispensed as surrogate markers for chronic illness.[14] The social status score (SSS) based on the patients' postal code was used as marker for individual social economic status (SES).[15] As proxy if the patient understood the information (domain 4) we used the relation between level of knowledge according to the pharmacist and the provision of information by the pharmacist.

We used linear mixed-effects models for continuous outcomes and generalized mixed-effect model with the logit link function for dichotomous outcomes both with pharmacy as random effect. A p-value of less than 0.05 was considered as statistical significant. For the descriptive analysis SPSS 20.0 was used and for multilevel analyses R software version 3.1.2. (Austria, www.R-project.org) using library *lme4* and *lmer* for continuous outcomes and *glmer* for dichotomous outcomes.

Results

The suggested strategies to improve treatment fidelity are discussed per domain of the BCC framework.

Fidelity on study design

Treatment fidelity on the study design aims at ensuring that the study adequately tests its hypotheses in relation to underlying theoretical and clinical processes.[8,9] Most strategies suggested by the BCC framework that improve fidelity on the design were implemented.

Prior to implementation of the trial, the protocols and manuals were reviewed by the research group and in a pilot in three pharmacies. In the treatment manual no information was provided of the maximum length of the call (#1a). Health care providers were instructed to counsel just once per patient (#1b). The health care providers received a detailed medication class specific interview protocol (#1c) (see appendix 2 of the trial protocol). This protocol was based on the Health Belief Model[11-13] (#4a) and contained additional items known to be important for patients.[16] The protocol was reviewed by two experts from the division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University involved in training and education of pharmacist trainees (#4b). Required credentials of the assigned staff member were not specified but the pharmacist was asked to assign a 'competent' employee (#3). No plan in case of setbacks was described in the trial protocol (#6).

Table 1: Suggested strategies to improve treatment fidelity on 'Study Design'.

Training health care providers	Score	Explanation
1. Provide information about treatment dose in the intervention condition		
a. Length of contact (minutes)	Absent	No limits are discussed
b. Number of contacts	Present	Described in protocol (1 contact)
c. Content of treatment	Present	Details in interview protocol
d. Duration of contact over time	N/A	
2. Provide information about treatment dose in the comparison condition	N/A	Comparison condition is usual care
3. Specification of provider credentials that are needed	Absent	'Competent' employee but without definition
4. Theoretical model upon which the intervention is based is clearly articulated		
a. The active ingredients are specified and incorporated into the intervention	Present	In instructions and interview protocol
b. Use of experts or protocol review group to determine whether the intervention protocol reflects the underlying theoretical model or clinical guidelines	Present	Two communication experts reviewed the protocol
c. Plan to ensure that the measures reflect the hypothesized theoretical constructs/mechanisms of action	Present	
5. Potential confounders that limit the ability to make conclusions at the end of the trial are identified?	Present	Confounders specified
6. Plan to address possible setbacks in implementation (i.e., back-up systems or providers)	Absent	No back-up system was described

Information of inclusion of patients

In 13 of 51 pharmacies the number of patients to include was reached and 8 pharmacies reached 75% of the goal. 17 of 29 pharmacies eligible for remuneration reached the 'remuneration goal'. Some pharmacists stopped including patients when the 'remuneration goal' was reached, irrespective of the study goal. In some pharmacies the inclusion of patients stopped temporarily due to drop out of the trained health care

provider. No data are available on the exact number of drop-outs and reasons for drop-out.

Fidelity on training health care providers

Treatment fidelity of pharmacist training involves standardizing training between health care providers, ensuring the delivery of the intervention as planned.[9] Three strategies were present. Per pharmacy one staff member received communication training which was described in the trial protocol[10] and included a pre- and post-training exam (#1,#2) however skill acquisition was not assessed (#3). All assigned pharmacy staff members in the first phase had to take the same course, irrespective of their experience and educational level (#7). Pharmacist trainees (BPharms) who participated in the second stage recently received similar training in the pharmacy curriculum and therefore did not follow the course (#7).[17,18] Length of the training was estimated at three hours but data were available neither for time actually spent on the training nor on the results of the exam. Pharmacies in the first phase could apply voluntarily and therefore are likely to be positive about the nature of the intervention and find the intervention acceptable and credible (#6) but pharmacist trainees in phase II were obliged to participate. Strategies like using observations, multiple training sessions or role-playing were not used.

Table 2: Suggested strategies to improve treatment fidelity on 'Training health care providers'.

Training health care providers	Score	Explanation
1. Description of how providers will be trained	Present	Training is described
2. Standardization of provider training (especially if multiple waves of training are needed for multiple providers)	Present	Standardized training (e-learning)
3. Assessment of provider skill acquisition	Absent	Knowledge tested, but skills not assessed
4. Assessment and monitoring of provider skill maintenance over time	Absent	Not assessed, but self-report had to be filled
5. Characteristics being sought in a treatment provider and ones that should be avoided in a treatment provider are articulated a priori	Absent	Not present but in instructions it was noted that providers had to be "competent"
6. At the hiring stage, assessment of whether or not there is a good fit between the provider and the intervention (e.g., ensure that providers find the intervention acceptable, credible and potentially efficacious	Present	Pharmacies in phase I could apply themselves. In phase II pharmacist trainees were obliged to participate
7. There is a training plan that takes into account trainees' different education and experience and learning styles	Absent/ present	Same course for all providers in phase I despite experience

Fidelity on delivery of treatment

Fidelity on delivery of treatment involves the assessment and monitoring of treatment competency (did the pharmacist maintain the skills over time?), treatment adherence (did the pharmacist follow the protocol?) and treatment differentiation (did the pharmacist only deliver the studied treatment?) (See Table 3).[8,9] For this domain of treatment almost all of the suggested strategies were implemented. A treatment manual was provided to ensure the content is delivered as specified (#5). Pharmacists received detailed instructions for the intervention and an interview protocol (#1). The online self-report they had to fill out for each patient supported fidelity on the delivery of treatment (#1, #2, #3, and #6). The strategy to assess non-specific treatment effects was also registered in the self-report (#4). Cluster randomization was used to prevent contamination and increase fidelity (#8).

Table 3: Suggested strategies to improve treatment fidelity on 'Delivery of Treatment'.

Domain: Delivery of Treatment	Score	Explanation
1. Method to ensure that the content of the intervention is delivered as specified	Present	Interview protocol and checklist were present
2. Method to ensure that the dose of the intervention is delivered as specified	Present	Interview protocol and checklist were present
3. Mechanism to assess if the provider actually adhered to the intervention plan or in the case of computer delivered interventions, method to assess participants' contact with the information	Present	Self-report had to be filled to register if and what the provider did
4. Assessment of non-specific treatment effects	Present	Additional interventions were registered
5. Use of treatment manual	Present	Treatment manual was provided
6. There is a plan for the assessment of whether or not the active ingredients were delivered	Present	Providers had to register online every participant including checklist
7. There is a plan for the assessment of whether or not proscribed components were delivered. (e.g., components that are unnecessary or unhelpful)	N/A	No components were proscribed and no limitations were set
8. There is a plan for how will contamination between conditions be prevented	Present	Cluster design plus automated selection queries
9. There is an a priori specification of treatment fidelity (e.g., providers adhere to delivering >80% of components)	Absent	Instruction was to follow the interview protocol, but no specification were made

Health care providers adherence to the protocol

Overall 55% of eligible patients were registered (see Table 4). The median registration rate per pharmacy was 48% (Interquartile range (IQR) 30% to 67%). Age, gender or CDS in registered patients was not different from patients without registration (Appendix 2). For 2,847 patients the online report was filled out; 919 of those patients did not meet the eligibility criteria. Of the remaining 1,928 patients, 64% (1,226) received the intervention, which is 68% of the pre-specified target of 1,800 patients. The most important reasons

why patients did not receive the intervention, were the absence of a telephone number (206), the patient could not be reached after a minimum of three attempts (193) or the patient refused counselling (89).

Table 4: Information on inclusion of patients.

	Arm A		Arm B		Overall
	Bisphosphonate	Antidepressant	RAS-inhibitor	Statin	
Median number of patients registered per pharmacy (IQR)	3 (1-11)	6.5 (2.5-47)	6 (3-13)	7 (2-15)	14 (5-35)
Eligible patients registered,% (n/N)	65 (244/378)	67 (890/1337)	45 (414/911)	42 (380/898)	55 (1928/3524)
Median registration rate per pharmacy, (IQR)	49 (40-62)	56 (44-70)	46 (25-55)	34 (25-53)	48 (30-67)
Eligible patients with intervention, % (n/N)	42 (160/378)	36 (478/1337)	34 (307/911)	31 (281/898)	35 (1226/3524)
Registered patients with intervention, % (n/N)	66 (160/244)	54 (478/890)	74 (307/414)	74 (281/380)	64 (1226/1928)
Number of pharmacies with:					
0-10 patients registered	17	13	20	16	22
11-30 patients registered	4	3	4	7	14
31-50 patients registered	2	3	1	3	4
>50 patients registered	0	5	2	1	11
Total	23	24	27	27	51

Older patients (≥65 year) were more likely to receive the intervention compared to younger patients (odds ratio (OR) 1.50 with 95% CI 1.28, 1.76). No significant relation was found for patients' social status score or gender. Patients starting with bisphosphonates or antidepressants who received counselling had a higher CDS score compared to non-called/non-registered patients, but corrected for age this difference was not significant (see Appendix 2).The average age of eligible patients was 56.3 (Standard Deviation (SD) 17.1) (see Table 5). In arm A (antidepressants/bisphosphonates) most interventions were delivered by the pharmacists (PharmD) while in arm B (antihypertensives/statins) the intervention was mostly delivered by the pharmacy practitioners.

Half of the patients were called at 15 days after the first dispense (IQR 9 to 25). This period increased in case patients could not be reached the first time. 50.2% of the patients were called within the defined time frame of 7-21 days after the start. For patients who were reached at the first attempt, 42% (20) of the pharmacies delivered the intervention for more than 75% of the patients within the pre-specified time interval of 7 to 21 days. The protocol instructed to try to reach a patient at least three times. On average 2.7 (SD 1.1) attempts were registered for the group of patients who eventually could not be reached. No differences between medication classes were found in number of attempts made.

Table 5: Patient and health care provider characteristics and information about delivery of treatment.

	Arm A		Arm B		Overall
	Bisphosphonate	Antidepressant	RAS-inhibitor	Statin	
Age, mean (SD), in years	68.4 (13.8)	49.9 (17.5)	61.7 (12.2)	62.5 (13.0)	56.3 (17.1)
Female, % (n/N)	78 (270/346)	61 (931/1538)	50 (249/496)	53 (249/466)	60 (1699/2846)
Educational level of provider (n)	132	374	254	245	1005
MPharm/PharmD, % (n)	50.0 (66)	54.8 (205)	19.7 (50)	22.0 (54)	37.3 (375)
BPharm/Bch, % (n)	14.4 (19)	29.9 (112)	66.5 (169)	63.3 (155)	45.3 (455)
Technician, % (n)	35.6 (47)	15.2 (57)	13.8 (35)	14.7 (36)	17.4 (175)
Time window					
Median number of days between first prescription and call, (IQR)	13 (6-20)	12 (6-17)	20 (13-29)	21 (14-30)	15 (9-25)
Proportion of patients reached within 7-21 days, % (n/N)	50.0 (66/132)	57.0 (213/374)	47.6 (121/254)	42.9 (105/245)	50.2 (505/1005)
Reasons for not providing intervention (n)	56	281	88	87	515
No telephone number available, % (n)	35.7 (20)	45.1 (128)	30.7 (27)	35.6 (31)	40.0 (206)
Patient could not be reached, % (n)	32.1 (18)	30.3 (86)	52.3 (46)	49.4 (43)	37.5 (193)
Patient refused counselling, % (n)	21.4 (12)	20.8 (59)	9.1 (8)	11.5 (10)	17.3 (89)
Patient was not, % (n) available or to sick	1.8 (1)	1.4 (1)	1.1 (1)	1.1 (1)	1.4 (7)
Other or missing, % (n)	8.9 (5)	2.5 (7)	6.8 (6)	2.3 (2)	3.9 (20)

On average 5.6 (SD 4.7) minutes were spent on the preparation and 8.3 (SD 4.4) minutes on the call itself. No differences in the duration of calls between medication classes were found, however compared to pharmacists both pharmacy practitioners and technicians stated to have spent less time per call (mean difference -1.3, 95% CI -2.3, -0.3) respectively (-2.3, 95% CI -3.6, -1.0).

Treatment differentiation: information on content

The self-reports filled out by the pharmacist provided information about the content delivered (item 1, 3 and 6; Table 6.) Although not all aspects presented below, relate to treatment fidelity, they do provide valuable information. According to the health care provider in 79.7% of the calls all five knowledge items were discussed. This proportion was lower for antidepressants compared to the other three classes ($p=0.02$, χ^2-test). The specific intake instructions for bisphosphonates were discussed in almost all calls (173 of 179) and specific information for antidepressants in 84% of the calls. In 66.6% of the calls all three potential barriers for medication intake that were included in the interview protocol were indeed discussed. If side effects were discussed, during the phone call 31.0% of the patients stated to experience side effects. Significantly more antidepressants

users experienced side effects compared to the three other medication classes (p<0.005, χ^2-test).

Health care providers indicated they provided additional information in 754 calls (62%). No differences were found between the four medication classes. However, compared to pharmacy practitioners more pharmacists (PharmD) stated to have provided information (OR 3.2, 95% CI 1.8, 5.4) but not compared to technicians (OR 0.7, 95% CI 0.4, 1.4). In 461 calls this information was about side effects, in 402 about the duration to the therapy, in 326 about the indication and in 154 about addiction to the medication.

Table 6: Discussion of knowledge and barriers during telephone call, % (n/N).

	Arm A		Arm B		Overall
	Bisphosphonate	Antidepressant	RAS-inhibitor	Statin	
All 5 knowledge items discussed	85.6 (113/132)	68.4 (256/374)	86.5 (212/245)	86.6 (220/254)	79.7 (801/1005)
All 3 barriers discussed	74.2 (98/132)	59.9 (224/374)	70.2 (172/245)	68.9 (175/254)	66.6 (669/1005)
Patient had concerns about dependence	1.8 (2/109)	11.8 (34/288)	5.5 (11/201)	6.0 (12/200)	7.4 (59/798)
Patient had concerns about side effects	15.6 (20/128)	22.6 (74/328)	15.6 (35/224)	13.1 (30/229)	17.5 (159/909)
Patient had doubts about necessity	6.9 (9/130)	11.6 (40/346)	11.6 (26/225)	8.9 (20/225)	10.3 (95/926)
Patient experienced side effects	15.7 (20/127)	48.8 (167/342)	21.0 (49/233)	23.3 (55/136)	31.0 (291/938)

Bold: p<0.05

In 73 calls the pharmacist stated to contact the prescribing physician mostly because of side effects (n=28). At least 19% of the patients (226/1,200) were advised to contact the physician, again mostly about side effects (50%) or regarding the indication for prescribing (9.7%). No differences were found between the four medication classes or educational level of assigned pharmacy staff member.

At the day of the call 81.5% of the patients stated to still use the medication, 10.1% started but already discontinued and 8.1% did not start (yet). The most important reasons not to start were fear of side effects (41.4%) and the fact that the patient felt better (10.4%). For 19.0% the reason for not starting was not registered.

Fidelity on receipt of the intervention

Fidelity of treatment receipt involves the assessment whether or not the delivered treatment was actually "received" by the patient[8,9] (See Table 7). Instructions were provided in the interview protocol to improve patients' comprehension of the intervention (#2) but patients' ability to perform the intervention skills were not assessed during the intervention period (#3). The receipt of treatment was assessed in a nested trial

of which the results have been published elsewhere[19]. With questionnaires, sent three months after the intervention, the satisfaction with information on medicines,[20] satisfaction with counselling, and beliefs about medicines[21] were assessed. Main results were that satisfaction on some information subjects were improved, patients valued the intervention and fewer patients had a sceptical attitude about the medication. The study also demonstrated that a part of the patients needed more information.

Table 7: Suggested strategies to improve treatment fidelity on 'Receipt of Treatment'.

Domain: Receipt of Treatment	Score	Explanation
1. There is an assessment of the degree to which participants understood the intervention	Not assessed	Subject of interview protocol
2. There are specification of strategies that will be used to improve participant comprehension of the intervention	Present	Instructions in the interview protocol
3. The participants' ability to perform the intervention skills will be assessed during the intervention period	Not assessed	This is not assessed during the intervention period but afterwards
4. A strategy will be used to improve subject performance of intervention skills during the intervention period	Not applicable	Intervention focused on the start only
5. Multicultural factors considered in the development and delivery (e.g., provided in native language; protocol consistent with values of target group)	Absent	Providers were allowed to address patients in native language but protocol was in Dutch

Pharmacists were instructed to assess if a patient understood the information (#1). As proxy for this assessment we used the relation between level of knowledge according to pharmacist and the provision of information. We found that the better the knowledge on a specific subject was according to the pharmacist, the less information was provided (see Figure 1). However, even when the knowledge was rated 'good', still extra information was provided in about 22% to 31% of these calls. On the other hand approximately 40% of the patients in whom knowledge was rated as bad, did not receive extra information according to the pharmacist. In Table 2 in Appendix 2 more information is shown about subgroup analysis.

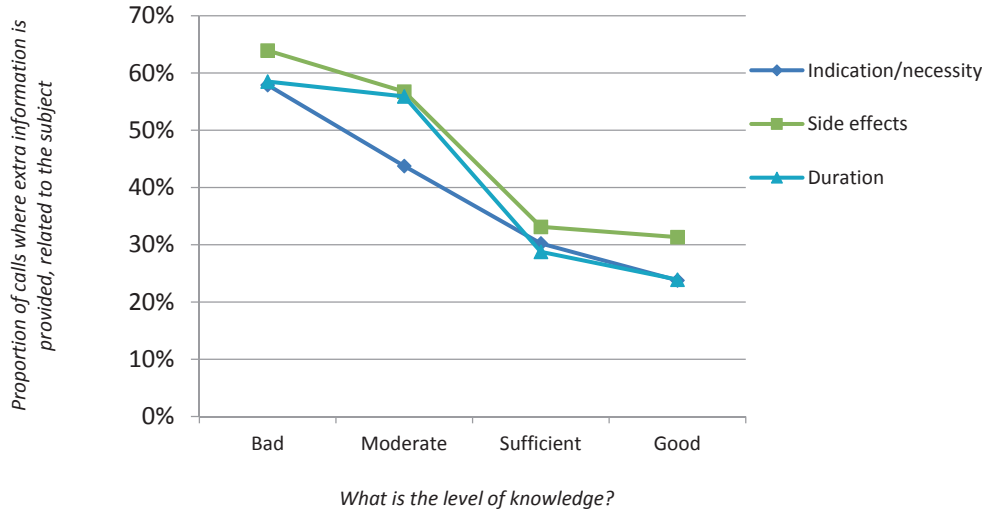

Figure 1: Relation between information provided and level of knowledge.

Multicultural aspects were not taken in to account. Although pharmacists could approach patients in a different language than Dutch, the interview protocol was not translated nor adapted to specific target groups (#5).

Fidelity on enactment of treatment skills

The last domain of the framework is the assessment and monitoring of whether or not patients actually use the information from the intervention. The intervention in this trial focussed on the initiation phase of treatment. Although medication adherence was the primary outcome of the study and adherence could be seen as ultimate enactment of treatment skills in the study, pharmacists did not monitor adherence during follow-up. Therefore there was no formal assessment of patients' performance of the intervention skills during the study.

Table 8: Suggested strategies to improve treatment fidelity on 'Enactment of Treatment Skills'.

Domain: Enactment of Treatment Skills	Score	Explanation
1 Participant performance of the intervention skills will be assessed in settings in which the intervention might be applied	Not assessed	
2 A strategy will be used to assess performance of the intervention skills in settings in which the intervention might be applied	Not assessed	

Discussion

In this study we assessed treatment fidelity of the telephone counselling intervention (TelCIP) on the domains suggested by NIH BCC framework.[9] On at least three domains the fidelity could be rated as sufficient: treatment design, delivery of treatment and receipt of treatment. The fidelity on training of health care providers was suboptimal and enactment of treatment skills was not assessed. The latter was a conscious decision since the primary goal was to study this intervention in a pragmatic, 'real-life' setting. The aim was to develop an intervention that could be relatively easy implemented in usual care. If pharmacists had to assess enactment of treatment skills by monitoring adherence, that also would have intensified the intervention making it more difficult for pharmacists to adhere to the intervention.

Exploration of the domain of 'receipt of the intervention' demonstrated that this was mostly assessed indirectly or using other patient related outcomes like satisfaction with information and beliefs about medicines. More intense assessment of receipt of treatment for example by assessing knowledge directly after the intervention with a questionnaire or an exit interview would have compromised feasibility and did not comply with the pragmatic nature of the intervention. Due to the registration of health care providers and the dispensing data, relevant information was available about the level of implementation. On average 55% of eligible patients were registered and 35% of the patients received the intervention. Little information is available from comparable studies. A review demonstrated a range in frequency of counselling from 29% to 69% at the start of therapy[1]. A trial in the Netherlands focussing on counselling for patients starting with statin therapy demonstrated that 15.5% of the patients received education at the first dispensing (EAFD) and 12.5% at the second dispensing (EASD).[22] Compared to this trial, telephone counselling can be helpful to improve counselling rates.

It is unknown why not all patients were selected for the intervention. Obvious pharmacy-related reasons are staff problems for example when the assigned pharmacist or pharmacy staff member went on maternity leave or holiday. Also technical issues can be involved: the selections had to be run weekly. When the pharmacist did not run the selection in a particular week, it was not possible to rerun the selection for that missed week and therefore patients were not selected when they started in that missed week. Since it was possible that pharmacists selectively registered patients, we compared characteristics of registered patients with non-registered patients. We found that they did not differ on relevant characteristics, although it cannot be ruled out that differences existed in unmeasured variables.

On most patient characteristics we found no difference between patients who were called and patients who were not called. However the results demonstrated that older patients

(≥65) were more likely to be reached than younger patients. In the Netherlands retirement age is 65 and a plausible explanation is that younger patients were less frequently at home during office hours.

This fidelity assessment has some limitations. Firstly, it is partially based on the reports of pharmacists, which may introduce a social desirability bias. Moreover, on some subjects it is based on the pharmacist's opinion about for example the level of patient knowledge. Some data were missing such as data on health care providers characteristics. Strategies on the original BCC questionnaire have to be rated as absent, present or not applicable. We found that in TelCIP some strategies were present, but insufficient. For example the interview protocol contained elements to assess if a patient understands the information, but it was unknown how well that was implemented. Lastly, the rating was performed by the study authors. It could have been improved when other, external researches would have assessed the implementation of the strategies.

Our study has strengths as well. With a structured approach of relevant aspects the treatment fidelity of the TelCIP trial was assessed. This provided insight in possible flaws and strengths of the intervention and detailed information on the implementation of the counselling. Another strength is that we were able to assess implementation rate linking dispensing data to the self-reports as filled out by the pharmacist. We were also able to perform analysis on patient characteristics using multilevel analysis techniques correcting for differences in cluster (size). An important finding was that no differences were found between registered patients and non-registered patients which implies a low risk of selection bias.

Conclusion

This self-assessment demonstrates that treatment fidelity on most aspect of the TelCIP trial was sufficient to good. Although not all pharmacists were able to include enough patients within the study period no indication for selection bias was found. Pharmacists followed the interview protocol in almost all phone calls, relevant subjects were discussed and information provided was tailored to the patient's level of knowledge or experienced barriers. Additionally the study provided knowledge about content of telephone counselling. Moreover, a relatively high proportion and number of patients was reached. The fidelity of the Telephone Counselling Intervention by Pharmacist overall can thus be rated as sufficient.

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Appendix 1: Online self-report for the assigned staff member

General information

- **Pharmacy identification code**
- **Position/educational level of assigned staff member**
- **Patient gender**
- **Patient year of birth**
- **Medication class**

Questions about the counselling

- **Counselling provided (Y/N). If not, most important reason for not providing intervention**
- **Total number of attempts**
- **Time spent on preparation**
- **Time spent on call**

Adherence

- **Did the patient start with the medication including most important reason to quit/ not to start (yet)**
- **Changes made in therapy (yes, no, unknown):**
  - ❑ In consultation with a doctor, the drug is replaced by another drug
  - ❑ In consultation with the doctor, the patient has stopped the therapy and no alternative is started
  - ❑ Without consulting the doctor, the patient discontinued with the therapy
  - ❑ The patient has changed the daily use without a consultation

Knowledge and barriers

- **Estimation of knowledge on the following subjects (good, sufficient, moderate, bad, not discussed):**
  1. The reason/indication to use the medication
  2. The mechanism of action
  3. The duration of treatment
  4. The correct moment of intake (for example in the morning, every day/week)
  5. Possible side effects
  6. For bisphosphonates: instructions: stay upright (don't bend or lie down) for the first ½ hour
  7. For antidepressants: the patient knows it takes 2-6 weeks to start working

- **Statements about possible drug related problems (totally agree, agree, agree/disagree, disagree, totally disagree, not discussed):**
  1. Patients has doubts about the necessity
  2. Patient experienced side effects
  3. Patient has concerns about side effects
  4. Patient has concerns about 'dependence'

Additional interventions/ advice provided

- **Any information provided? Y/N**
- **Which advices have been given during the call?**
  - ❑ Advice related to the intake of the medicine
  - ❑ Explanation of the duration of the therapy
  - ❑ Explanation/motivation of the indication
  - ❑ Explanation of possible side effects
  - ❑ Explanation possible dependence
  - ❑ Other, _____

- **Any additional interventions:**
  - ❑ Pill timer provided
  - ❑ Drug intake schedule provide
  - ❑ Sign up for chronic medication service
  - ❑ Sign up for weekly dose system
  - ❑ Other, _____
- **Pharmacist will contact physician with**
  - ❑ Suggestion to switch to other medication
  - ❑ Suggestion to stop with the medication
  - ❑ Suggestion to change the dose
  - ❑ Suggestion to start other medication
  - ❑ Other
- **Patient advised to contact physician regarding**
  - ❑ Side effects
  - ❑ Reason/indication is not clear to the patient
  - ❑ Practical problems
  - ❑ Other
- **Additional information:**

Appendix 2: Additional results

Table 9: Differences in age, chronic disease score, status score and gender between registered versus non-registered patients and called versus non-called patients.

Medication class	Registered versus non-registered Effect size (95% CI)	Called versus non-called Effect size (95% CI)
Age		
RAS-inhibitors	-0.10 (-1.88,1.68)	**2.57 (0.72,4.42)**
Statins	-0.70 (-2.21,0.81)	1.26 (-0.33,2.86)
Bisphosphonates	**3.28 (0.35,6.22)**	**3.48 (0.66,6.30)**
Antidepressants	2.00 (-0.01,4.02)	**4.19 (2.30,6.08)**
Chronic disease score (CDS)		
RAS-inhibitors	0.14 (-0.28,0.56)	0.39 (-0.06,0.84)
Statins	0.13 (-0.27,0.52)	0.33 (-0.09,0.76)
Bisphosphonates	0.53 (-0.32,1.38)	**0.97 (0.12,1.82)**
Antidepressants	0.13 (-0.24,0.50)	**0.38 (0.005,0.76)**
Status score		
RAS-inhibitors	**-0.11 (-0.22,,0.003)**	-0.09 (-0.20,0.02)
Statins	-0.04 (-0.14,0.06)	-0.02 (-0.12,0.08)
Bisphosphonates	0.07 (-0.13,0.26)	0.03 (-0.16,0.22)
Antidepressants	0.002 (-0.12,0.13)	0.05 (,0.06,0.16)
Gender (female)		
RAS-inhibitors	1.25 (0.93,1.66)	1.27 (0.94,1.70)
Statins	1.05 (0.79,1.40)	1.24 (0.93,1.66)
Bisphosphonates	1.22 (0.69,2.17)	1.24 (0.72,2.14)
Antidepressants	0.91 (0.70,1.20)	1.01 (0.79,1.30)

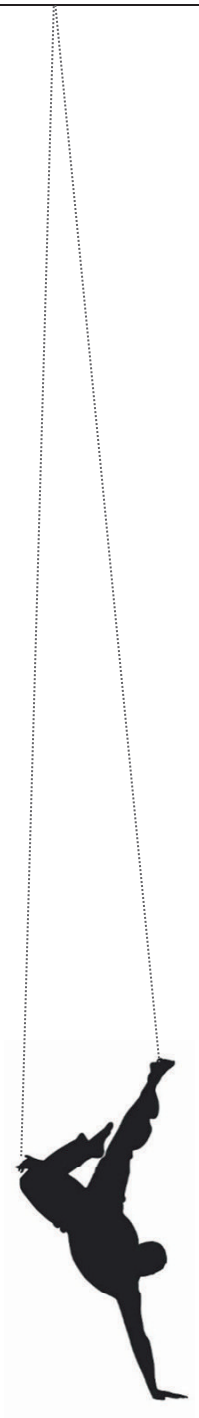
Effect size is mean difference for age, chronic disease score and social status score and odds ratio for gender.
Significant effects are printed in bold.

Table 10: Relation between level of knowledge and provision of information.

	Unadj. Effect size (95% CI)	Adj*. Effect size (95% CI)
Relation between level of knowledge about indication and provision of information about indication		
Medication class		
Overall	**2.07 (1.62,2.63)**	**2.12 (1.65,2.73)**
RAS,inhibitors	**1.65 (1.09,2.52)**	**1.73 (1.11,2.71)**
Statins	**2.06 (1.19,3.56)**	**2.18 (1.24,3.83)**
Bisphosphonates	**3.06 (1.69,5.52)**	**3.13 (1.62,6.03)**
Antidepressants	**2.06 (1.32,3.23)**	**2.32 (1.46,3.71)**
Educational level pharmacy staff member		
PharmD	**2.80 (1.78,4.40)**	**3.05 (1.88,4.96)**
Pharmacy practitioner	**1.83 (1.25,2.69)**	**1.87 (1.27,2.76)**
Technician	**1.75 (1.08,2.84)**	**1.72 (1.06,2.79)**
Relation between level of knowledge about duration and provision of information about duration		
Medication class		
Overall	**2.37 (1.93,2.92)**	**2.40 (1.94,2.97)**
RAS,inhibitors	**2.52 (1.53,4.16)**	**2.47 (1.49,4.12)**
Statins	**2.39 (1.43,3.98)**	**2.65 (1.55,4.52)**
Bisphosphonates	**2.79 (1.62,4.81)**	**2.77 (1.58,4.86)**
Antidepressants	**2.34 (1.74,3.15)**	**2.34 (1.73,3.17)**
Educational level pharmacy staff member		
PharmD	**2.24 (1.61,3.10)**	**2.32 (1.66,3.26)**
Pharmacy practitioner	**2.39 (1.72,3.33)**	**2.43 (1.74,3.39)**
Technician	**2.49 (1.48,4.20)**	**2.46 (1.45,4.17)**
Relation between level of knowledge about side effects and provision of information about side effects		
Medication class		
Overall	**1.66 (1.37,2.01)**	**1.70 (1.40,2.06)**
RAS,inhibitors	1.40 (0.95,2.05)	1.40 (0.96,2.06)
Statins	1.36 (0.92,2.00)	**1.35 (1.16,1.58)**
Bisphosphonates	**3.19 (1.77,5.78)**	**3.25 (1.77,5.97)**
Antidepressants	**1.83 (1.33,2.53)**	**1.88 (1.35,2.61)**
Educational level pharmacy staff member		
PharmD	**2.44 (1.64,3.64)**	**2.60 (1.71,3.95)**
Pharmacy practitioner	**1.31 (1.01,1.69)**	**1.33 (1.02,1.74)**
Technician	**2.15 (1.37,3.37)**	**2.09 (1.32,3.30)**

* Adjusted for age, medication class, educational level HCP and CDS.

Significant effects are printed in bold.



CHAPTER 4.3

Telephone counselling: pharmacists exploring adherence, practical and perceptual barriers and information needs at the start of therapy

Marcel J. Kooy, Annemiek J. Linn, Eibert R. Heerdink, Liset van Dijk, Marcel L. Bouvy

Abstract

Objective: Counselling can improve adherence to medication. Health care providers often do not explore adherence with their patients. As part of an intervention study, this this study primarily aims to assess to what extent pharmacists explore adherence, practical and perceptual barriers and information needs at the start of therapy.

Methods: Patients initiating either antidepressant or bisphosphonate were contacted by a pharmacist by telephone within two weeks after the start of the treatment. Pharmacists used a semi-structured interview protocol and recorded the telephone calls.

Results: In five pharmacies 31 calls were recorded. Five patients did not use the medication (anymore). In virtually all calls barriers (n=27) and the need for information (n=29) were explored at least once. Most barriers expressed by patients were practical and mostly in relation to side effects. In 7 calls the pharmacist explicitly explored the presence of perceptual barriers. About half of the patients expressed an information need.

Conclusion: Pharmacists using an interview protocol are able to address practical barriers and need for information with patients in telephone counselling. Perceptual barriers are less often discussed.

Practice implications: Counselling by telephone can be used to explore information needs and practical barriers to adherence. Special attention should be given to the explicit exploration of perceptual barriers.

Introduction

Patient counselling, including education and behavioural support, has been shown to be effective in improving adherence to medication.[1-4] For many patients, open communication about barriers to medication adherence, obtaining information needs and feeling supported may lead to improved adherence.[4] Proper counselling by health care providers encompasses tailoring of information to the patients' needs,[5-7] assessment of patients' understanding, and exploration of barriers that may decrease adherence.[8] Pharmacists play a role in counselling and in improving adherence.[9-11] In particular the contact at the first and second refills are excellent opportunities to discover non-adherence, medication related barriers and information needs[12,13] since discontinuation rates in the first months can be high.[13-15]

Health care providers however often fail to talk about at least three important subjects at start of therapy related to medication: (non-)adherence, barriers to adherence and information needs.[16] Regarding the first topic, providers find if often difficult to discuss non-adherence, which then remains undetected,[16,17] despite evidence that the majority of patients believe that talking with their health care provider about their medication is useful. Considering the barriers, observational studies show that health care providers do not always encourage patients to express their barriers for not taking the medication as prescribed.[8,16,17] Yet, research shows that patients are happy to discuss their concerns about their medication when encouraged to do this in an appropriate way.[17] Lastly, health care providers often do not explore patients' information needs sufficiently.[18,19] It has been suggested that patients do not clearly express their information needs because they either assume that the provider has told them everything or because they do not want to appear ignorant or take up too much time of their provider.[20,21] Yet, patients often report unmet informational needs when starting their medication.[18,22] Moreover, health care providers are often not able to properly address patients' information needs.[7]

Considering the relevance of adherence to medication and the fact that non-adherence, barriers and information needs often are not discussed, we designed an intervention study aimed at improving adherence of which the design has been published before.[23] To make conclusive statements about the effect of this health behaviour intervention it is important to assess if the intervention is implemented as planned.[24,25] The aim of this study is to provide more insight in how the intervention is delivered by assessing to what extent and how pharmacists actually explored adherence, practical and perceptual barriers and patients' need for information.

Methods

The presented qualitative study is part of the larger Telephone Counselling Intervention by Pharmacists (TelCIP).[23] This cluster randomized controlled trial studies the effect on adherence of telephone counselling by pharmacists in patients starting treatment. In this sub-study, we focused on how (non-)adherence, barriers and information needs were explored during these telephone counselling sessions.

Design and population

Five pharmacies participating in the TelCIP-trial and located in different areas of the Netherlands participated in this nested study. Patient inclusion criteria were: 1) aged 18 or older, 2) initiating therapy with an antidepressant or bisphosphonate (for treatment/prevention of osteoporosis), 3) responsible for their own medication intake, 4) not switching to other medication within the same pharmacological group in the 12 months before inclusion, and 5) speaking Dutch. These two medication classes are chosen since adherence rates are low[26,27] and patients often only experience the long-term benefits. Antidepressants were also chosen because most patients experience side effects that probably disappear after a couple of weeks while it takes up to six weeks to experience the positive effect. Bisphosphonates were also chosen because these need specific instructions for use (sit/stand up straight for at least half an hour).

Intervention

The intervention consisted of telephone counselling 7-21 days after the start of a new treatment. The purpose of the counselling call was to detect non-adherence, address practical and perceptual barriers and assess information need. To support the call, a medication class specific interview protocol was provided (see trial protocol for the generic version).[23] This protocol was based on the Health Belief Model (HBM). The HBM suggests that adherent behaviour is influenced by perceived severity of the disease and the perceived effects and disadvantages of the advised behaviour.[28-30] Items known to be important were also incorporated.[22] This protocol was reviewed by two experts from the department of Utrecht University involved in training and education of pharmacist trainees.

The pharmacists received communication training aiming to increase the understanding of the behaviour and barriers of patients related to medication intake. The training took about three hours, including case studies and a test to assess the theoretical knowledge on effective communication. Pharmacists received a voice recorder and were instructed to record the phone call. At the end of the inclusion period the recorders were collected.

Ethics

The Medical Ethics Review Committee (METC) of the University Medical Centre Utrecht concluded that the TelCIP trial was not subject to the regulations of the Medical Research Involving Human Subjects Act. Patients in the intervention arm meeting all eligibility criteria received an information letter, were invited for the study participation and were asked for informed consent. The TelCIP trial was registered at www.clinicaltrials.gov under the identifier NCT00493337. The Institutional Review Board of the division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University approved an amendment that described recording the telephone consultations. Patients were asked for verbal permission to audio record the consultation with their pharmacist.

Analysis

The recorded consultations were transcribed verbatim. Two researchers (MK and AL) analysed the data. Categories were discussed by both researchers to ensure consistency of interpretation. Disagreements between researchers were resolved through discussion and if necessary a third author was involved. For the analysis of the transcripts, we derived guidelines from qualitative literature.[31,32] The MAXQDA 2007 software was used for coding and analysis. The first step of the analyses involved the close reading and re-reading of transcripts. The second step was open coding. The third step is commonly referred to as focused coding. We made an inventory of main aspects that were related to the exploration of patients' barriers, experiences and information needs/knowledge. Subsequently we looked for possible categories within this inventory. We inductively derived three main categories from the data. Below, results are summarized per category. Per category we coded if the pharmacist was exploring the subject and/or if the patient was expressing the subject. For example if a patient mentioned to the pharmacist that he/she stopped using the medication, we coded it as 'patient expressing non-adherence' and if a pharmacist asked if a patient was using the medication, we coded it as 'pharmacist exploring adherence'.

Results

In total 31 patients from 5 pharmacies were included. Most patients were female (64.5%) and the average age was 52.6 years (Standard Deviation (SD) 19.0). Eight patients started with a bisphosphonate and the other 23 patients started with an antidepressant. Seven patients did not provide permission to record the call.

In total 325 fragments were coded in three subject categories (a) discussing adherence, (b) discussing barriers and (c) discussing information needs (see Table 1 and 2). The number of calls and fragments in which the pharmacist explored the particular subject

('Pharmacists exploring') are presented in Table 2 as well as the number in which the patient suggested or explicitly expressed (a) non-adherence, (b) the experience of barriers and (c) need for information.

Table 1: Derived categories.

	Category	Description	
		Pharmacists exploring	Patients expressing
Adherence	Adherence to long-term therapy is generally defined as the extent to which a person's behaviour (e.g. taking medication) corresponds with agreed recommendations from a healthcare provider	The pharmacist explores whether the patient is taking the medication as prescribed. This included both if and how the patient is using it	The patient expresses not to take the medication as prescribed (non-adherence). This includes fragments in which the patient indicates not to be using the medication (anymore) or taking it not according to the instructions
Barriers	*Practical barriers:* The patient is experiencing side effects, lack of experienced effect, remuneration of costs, difficulty with taking medication (for example with opening the bottle) *Perceptual barriers:* The patient is experiencing concerns about medication including fear for side effects, doubts about indication, low necessity beliefs	The pharmacist explores the patient's practical and/or perceptual barriers to adherent behaviour	The patient expresses practical and/or perceptual barriers to adherent behaviour
Information needs	Information needs can be explicit or yet unrecognized: patients can have specific questions or could be unaware of the importance of certain information	The pharmacist explores whether the patient need information, has questions about the medication and if the knowledge is sufficient	The patient seems to have insufficient knowledge (i.e., a patient doesn't know for how long the medication should be used) or explicitly expresses a need for information. (e.g. about the duration or indication of the therapy)

Table 2 also shows if the expression of patients is in direct response to prior exploration of the pharmacist. Most fragments where coded as 'exploring information needs' (n=98) followed by 'exploring barriers to medication intake' (n=83), 'exploring medication adherence' (n=62) and 'expressing barriers' (n=55).

Table 2: Frequency of coded fragments and number of calls in which a specific subject.

Subject category	Pharmacists exploring		Patients expressing			
			Total		In reaction to exploration of pharmacist	
	No. of fragments*	No. of calls#	No. of fragments*	No. of calls#	No. of fragments*	No. of calls#
Discussing adherence	62	27	8	5	2	1
Discussing barriers - total	83	28	55	26	37	19
• Barriers - practical	67	27	43	21	33	17
• Barriers - perceptual	11	7	12	8	4	2
Discussing information needs	98	29	27	18	21	16

* Number of fragments coded.

Number of patients (calls) in which a fragment has been coded.

Discussing adherence

In all recordings (n=31), patients and pharmacists discussed adherence. In 27 calls the pharmacist explicitly explored adherence. For example by asking “Did you already start with your medication?” or “Please tell me how you take your medication”. If pharmacists explored medication intake behaviour, they mostly referred to the frequency of taking the medication by asking when patients use their medication or for how long they have used their medication: “On which day do you take your medication?” or “When do you take your medication?”. Most patients told the pharmacists that they took the medication as prescribed “I always take my medication in the evening, just as the doctor told me.” A total of five patients expressed not to use the medication: three patients told the pharmacist that they did not start with the medication and two patients started but already stopped. For example one patient said: “To be honest, I didn’t start taking them.” Pharmacist reacted differently on this expression of non-adherence. Sometimes the pharmacist assessed the barriers extensively while in other calls the pharmacist more or less neglected the remark of the patient.

Discussing barriers

In 27 out of 31 calls the pharmacist explored barriers. Practical barriers were explored in 21 calls for example by asking “What are your experiences with this medication?”. In seven calls also perceptual barriers were explored: “How do you feel about using this medication?” Sometimes the pharmacist explicitly mentioned the most common side effects for the particular drug, which were all calls by the same pharmacist. In five fragments the pharmacist explored barriers in a general way and did not refer to possible practical or perceptual barriers. For example by asking: “Do you have trouble using this medicine?” In this case patients could react by expressing practical and/or perceptual barriers.

In most calls (26 out of 31) patients expressed at least one barrier. Most practical barriers related to side effects. In total, 18 patients mentioned the experience of side effects, three patients mentioned that they did not experience any positive effect yet and two patients said they temporarily could not use the medication due to comorbidity. Eight patients expressed perceptual barriers, mostly related to concerns about possible side effects: “I am using medication for over 20 years, taking medication destroys my organs and my body” or “When I woke up, I felt really stiff and then I thought, this is worse than what I have” and Some patients explicitly mentioned that the (risk of) side effects did not outweigh the necessity: “I have read the information leaflet, but it is not worth it.”

Discussing information needs

In 29 of the 31 calls the pharmacist assessed patients’ knowledge and the need for (more) information. Pharmacists used questions such as: “Why do you have to use this medication?” or “Did the physician tell you how long you have to use it?” At the end of most calls (n=25) the pharmacist asked if the patient had any questions: “Do you have any questions?” or “Is everything clear for you?” Moreover, pharmacists invited patients to contact them if they have any questions after the call: “If questions arise afterwards, you can always contact the pharmacy.” In two calls the pharmacist did not explicitly assess any need for information or lack of knowledge but provided information anyway.

In response to the exploration by the pharmacist, 16 patients indicated lack of knowledge or need for information. Patients did not know how long they should take their medication: “I have no idea. I just know that I need to get a new bone scan after three years and they did not tell me how long I have to use them.” Other information gaps reported by the patient were: 1) why the medication was prescribed; 2) side effects; 3) when to use it; 4) when patients can expect an effect; 5) interactions with other medication. Four patients explicitly asked for more information without prior exploration by the pharmacist.

Differences between pharmacists and between medication groups

Although it was not the objective of this study to make comparisons between pharmacists and between the two medication classes, we noticed some similarities and some differences. One pharmacist explicitly listed the most common side-effects one-by-one and asked the patients if they suffered from that side effect. For one patient this strategy led to the identification of a side effect that the patient had not yet attributed to the medication, which led to the identification of a barrier. Also the level of exploration of barriers was different between pharmacists. Some pharmacists explicitly explored

perceptual barriers while others did ask the patient about their opinion but directly asked a second question. This resulted in the patient only answering the second question.
Some pharmacists used more open questions to assess barriers or any lack of knowledge compared to other pharmacists. In one pharmacy we found less fragments indicating exploration of knowledge gaps than in other pharmacies.
Most patients using antidepressants uttered at least one barrier (22 of 23 patients). Of the 8 patients using a bisphosphonate 4 patients mentioned at least one barrier.

Discussion and conclusion

Discussion

This study shows that pharmacists who are provided with an extensive interview protocol, explored patients' adherence, barriers and information needs when they deliver telephone counselling about two weeks after the initiation of pharmacotherapy. Whereas practical barriers were discussed in almost every call, perceptual barriers were discussed in less than one third of the calls. Given that perceived concerns about the medication play an important role in non-adherence[33] exploring and responding adequately to patients' concerns is essential. Pharmacist should be provided with a more extensive training program focused on how they can explore patients' perceptual barriers and which communicative techniques should be used to address perceptual barriers to adherence.
Some patients stopped using the medication or did not even start using it. Results indicated that patients were willing to discuss this with the pharmacist. Research in general practitioners and hospital setting showed that it seems to be rather difficult to discuss non-adherence; both the provider and patients refrain from putting the topic high on the agenda.[8,16,34] This is a well-known and resistant problem and requires adequate provider-patient communication. Our study demonstrates however that it is feasible to discuss adherence when using a protocol. As intended, most pharmacists explored practical barriers to medication intake. Research into communication about medication by health professionals suggests that most consultations fall short in exploring these barriers.[8,16,17] Results showed that almost two third of the expressed barriers were in direct relation to the exploration of the pharmacist. A study that also used a short interview protocol to detect barriers to medication intake at the start of therapy led to the reporting of side effects or ineffectiveness in 22% of contacts.[13]
Practical barriers (i.e. side effects) were mentioned most often by patients. If patients expressed perceptual barriers, these often were related to concerns about side effects and doubts about the need to take the medication. Similar results were found in a study involving 23 community pharmacies in England. More than half of the patients, who started their medication, reported at least one barrier to medication intake. Most

reported barriers were side effects, concerns and difficulties with practical aspects of taking medication.[7] Fear of adverse effects and the actual occurrence of adverse effects are the main reasons for not accepting treatment with SSRI, a group of antidepressants.[35] To improve adherence, it is important that providers talk about these barriers.

If patients do not know why they have to take the medication, this will lead to non-adherence.[7] Pharmacists have the potential to fulfil these information needs when dispensing medication.[18,36,37] However, patients' needs are often not met.[7,18,36] Using a semi-structured interview protocol resulted in exploration of the patients' information needs in almost all calls. A protocol seems to be a feasible tool when exploring patients' information needs. Although we achieved theoretical saturation (no new themes emerging), a limitation of this study is that we had a relatively small sample patients who are using antidepressant or bisphosphonate. Since medication related problems may differ per medication, future research should include other types of medications. Another limitation is related to the procedure of this study; pharmacists called the patient to ask whether (s)he wanted to participate. Only if the patient agreed, audiotaping started. We do not know what has been discussed before the consultation was recorded or what was discussed with seven patients who refused recording.

Strength of our study is that we used audio recordings of the conversations. Qualitative studies examining the nature of pharmacists (telephone) counselling interactions are scare. Our data allowed direct analysis of communication without relying on participant reports or simulated situations.

Although counselling by telephone is not ideal for every patient, it has some advantages; the patient is in his or her own safe environment and the counselling can take place at a moment that suits the patients. Moreover a previous study showed that if counselling is provided by phone, pharmacists are more willing to implement these consultations in their daily practice as compared to face-to–face.[38] Counselling by telephone is easier to implement since the calls can be scheduled, competent employees can be appointed and better anticipate on the subject and language barriers. In addition our study demonstrates that pharmacist address relevant subjects during telephone counselling.

Conclusion

The study shows that pharmacists using an interview protocol frequently explore adherence, practical barriers and need for information when they call patients after the start of therapy. Perceptual barriers, however, are often not explicitly explored by the pharmacist. Some pharmacist explored more extensive than others. In most calls the main subjects of the interview protocol were discussed.

Practice implications

More attention should be given to the assessment of perceptual barriers. Discussing perceptual barriers might be improved by providing training programs to pharmacist in how to identify perceptual barriers to medication adherence and how to respond to it. Audio recordings of counselling calls can be helpful in this training. Nevertheless, calling patients at the start of therapy is helpful to assess practical barriers, non-adherence and information needs. This intervention is relatively easy to implement and the protocol can help to discuss the relevant subjects.

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CHAPTER 4.4

Patients' general satisfaction with telephone counselling by pharmacists and effects on satisfaction with information and beliefs about medicines: results from a cluster randomized trial

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Abstract

Objective: Assess effects of pharmacists' counselling by telephone on patients' satisfaction with counselling, satisfaction with information and beliefs about medicines for newly prescribed medicines.

Methods: A cluster randomized trial in Dutch community pharmacies. Patients ≥ 18 years where included when starting with antidepressants, bisphosphonates, RAS-inhibitors or lipid-lowering drugs. The intervention comprised counselling by telephone to address barriers to adherent behaviour. It was supported by an interview protocol. Controls received usual care. Outcomes were effects on beliefs about medication, satisfaction with information and counselling. Data was collected with a questionnaire.

Results: Responses of 211 patients in nine pharmacies were analysed. More intervention arm patients were satisfied with counselling (adj. OR 2.2, 95% CI 1.3, 3.6). Patients with counselling were significantly more satisfied with information on 4 items, had less concerns and less frequently had a 'sceptical' attitude towards medication (adj. OR 0.5, 95% CI 0.3, 0.9). Effects on most outcomes were more pronounced in men than in women.

Conclusions: Telephone counselling by pharmacists improved satisfaction with counselling and satisfaction with information on some items. It had a small effect on beliefs about medicines.

Practice implications: Pharmacists can use counselling by telephone, but more research is needed to find out which patients benefit most.

Introduction

Patients starting medication need information about their medicines to support appropriate and safe use.[1-5] This includes practical instructions on usage but also information about possible side effects, the expected pharmacological action and what happens if a patient does not take the medication.[2,6,7] This information should improve patients' understanding of the expected benefits and risks.[3,8]

Physicians and pharmacists play an important role in providing counselling about benefits, risks and correct use of medication.[9] In counselling-sessions a health care provider can tailor information to the patients' needs,[5,10,11] assess whether a patient understands the information and also assess barriers that may negatively influence adherence to medication.[12]

Counselling, including education and behavioural support, can improve medication adherence.[13] Adherence to long-term therapy is generally defined as the extent to which a person's behaviour (e.g. taking medication) corresponds with agreed recommendations from a health care provider.[14] Adherence to medication for long-term treatment is low,[14-17] which severely compromises the effect of the therapy. Dutch pharmacy guidelines recommend education and counselling at the pharmacy including exploration of lack of knowledge, information needs and experiences with the medication. The first period after the start of treatment is especially important since discontinuation of therapy is highest in the first weeks after the start of a new treatment.[18]

In daily practice not all patients starting with medication receive optimal care from physician[19] or pharmacists.[20] Studies show that information needs of patients are not always met[6,7,21,22] and that barriers to adherent behaviour are not always assessed.[12,23,24] The quality of communication can be improved,[25,26] also because part of the information is forgotten or remembered incorrectly.[27]

Considering barriers that hamper implementation of counselling in pharmacies,[28,29] a feasible alternative to face-to-face counselling may be counselling by telephone.[30] This has been proven to improve adherence measured after 4-week follow-up and to be effective in reducing mortality in non-adherent patients.[31]

We designed the TelCIP trial, a cluster randomized controlled trial in patients starting with antidepressants, antihypertensives, lipid lowering drugs or bisphosphonates to study the effect of counselling by telephone on medication adherence.[32] Cluster randomization was chosen as this was supposed to increase feasibility of implementation of the study protocol in pharmacies and to reduce the risk of contamination.

In the counselling calls the pharmacists assess and address possible barriers including lack of knowledge, concerns about medication and low necessity beliefs. Our hypothesis is that this type of counselling will improve knowledge, reduce concerns about medication and

improve necessity beliefs. This may ultimately improve medication adherence. Although this effect of the intervention on adherence is important, it is as important to assess the impact on the pathway that ultimately leads to adherent behaviour. This is because it is this pathway where the pharmacist addresses the needs of each individual patient and where the actual intervention takes place. Therefore the objective of the present study is to assess the effect of a telephone counselling intervention at the start of pharmacotherapy on patients' (1) general satisfaction with counselling, (2) satisfaction with information and (3) beliefs about medicines.

Methods

This study is part of a cluster randomized controlled trial of which the trial protocol has been published before.[32]

Setting & population

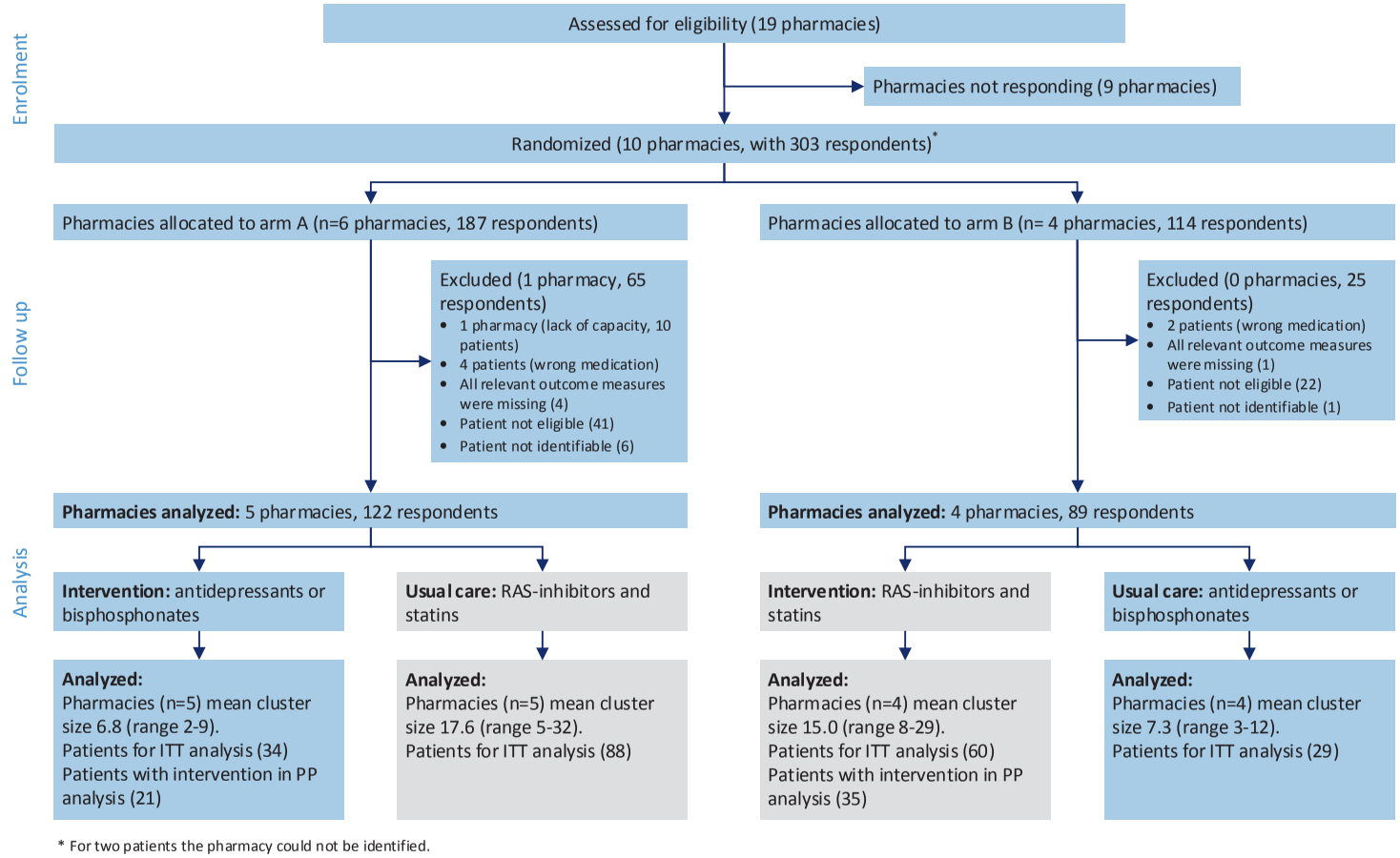
This study was conducted in community pharmacies in various parts of The Netherlands. Pharmacists could apply for participation by a website and after consenting the pharmacies (clusters) were randomly allocated by a researcher (MK) to either study arm A or study arm group B (Figure 1) in a 1:1 ratio. All pharmacists had to provide the intervention; pharmacies in arm A for patients starting with antidepressants and bisphosphonates and in arm B for RAS-inhibitors and lipid-lowering drug. Given the nature of the study design it was impossible for both pharmacists and researchers to be blinded to the group assignment.

Patients of 18 years or older were selected if they filled a first-time prescription for an antidepressant, a bisphosphonate, an antilipaemic or a Renin-Angiotensin-System (RAS) inhibitor. Patients were excluded if they were not responsible for their own medication or if they received medication in multi dose dispensing systems.

For technical reasons only pharmacies participating in the TelCIP trial using a specific pharmacy information system were asked to participate in this sub study. The nine pharmacies that participated in this sub study were located in various parts of the Netherlands, both rural and urban areas.[32]

Intervention arms

In addition to usual care, patients in the intervention arm received the intervention consisting of telephone counselling by the pharmacist. An interview protocol was developed to support the pharmacists in counselling patients on the following topics: 1) actual medication intake 2) practical and perceptual barriers related to medication use (including side effects) and 3) information needs and lack of knowledge about the



* For two patients the pharmacy could not be identified.

Figure 1: Participant flowchart.

medication, which has been published as additional file to the trial protocol.[32] When needed the pharmacist provided information, motivated the patient to keep using the medication, suggested strategies to adhere to the medication regimen and if necessary referred the patient to the physician. After the call, the pharmacists had to register the content of the call in an online form.

All participating pharmacists received an e-learning communication training based on the Health Belief Model (HBM) which is described in more detail in the study protocol.[32] The HBM suggests that adherence behaviour is influenced by perceived severity (beliefs about how severe the condition is), perceived susceptibility (the extent to which the patient feels at risk of suffering from the condition) and the expected beneficial effects and perceived disadvantages of the advised behaviour.[33,34]

Usual care

Dutch pharmacy guidelines recommend counselling when a first prescription for a new medication is filled. This first fill provides for a maximum of two weeks. Guidelines recommend additional counselling at the first refill. This refill counselling should include exploration of patients' needs and experiences with medication. However as mentioned before, these guidelines are not always properly implemented in daily care.[29]

Outcome measures

Outcomes were measured at patient level. Patients in both arms received one questionnaire three months after the first prescription. The inclusion period was not the same for all clusters but overall questionnaires were sent from August 2011 till December 2012. Questionnaires were sent three months after the first prescription and contained socio-demographic questions and questions on general satisfaction with counselling, satisfaction with information and beliefs about medicines (see below). Patients were asked about the reason for use of the medication in an open question and three authors (MK, RH, and MB) independently categorized the answers in the most plausible indication. Authors were blinded for group allocation and disagreements between authors were resolved by discussion.

General satisfaction with counselling

Patients were asked to rate their general satisfaction with pharmacy counselling in the preceding three months. Four questions from the Consumer Quality Index (CQI) were used aiming to assess different aspects of pharmaceutical care.[35] The following questions were used: (1) "Did the pharmacist or technician ask you about your experiences with the medication?", (2) "Did the pharmacist or technician ask you if you suffered from any side

effects?", (3) "Did the pharmacist or technician provide enough personal counselling?" and (4) "Did the pharmacist or technician ask you if you manage to take your medication as prescribed?" For each question, three answer options were offered: "yes", "no" or "I don't remember".
In addition, in the intervention arm patients' satisfaction with telephone counselling was assessed with four questions: "Do you appreciate this service?", "Do you think it has an added value?", "Would you like to be called next time you start with a medicine?" and "Do you prefer face-to-face counselling over telephone counselling?"

Satisfaction with information
The Satisfaction with Information about Medicines Scale (SIMS) was used to assess the satisfaction with the information provided on particular aspects of medicine use.[3] We used 9 of the 17 items of the original questionnaire (see appendix) because some items were not relevant for all four groups of medication and we aimed to study the effect of the intervention on particular aspects of information about medicines that were likely to be addressed during telephone counselling.[20] Patients were asked to rate the amount of the information received on the following response scale: "too much", "about right", "too little", "none received" and "none needed". Patients answering "about right" were labelled as satisfied.

Beliefs about medicines
High concerns about medication or low necessity beliefs negatively influence adherence to medication.[8] A method to assess the necessity beliefs and concerns patients have about medication is offered by the Necessity-Concerns Framework and can be valued with the Beliefs about Medicines Questionnaire - specific (BMQs).[36] The BMQs measures both the perceived necessity and concerns about prescribed medication. Both scales consist of five items and each item is scored using a 5-point Likert scale (1=strongly disagree to 5=strongly agree); therefore the individual score per scale ranges from 5 to 25. A necessity-concerns differential is calculated by subtracting the concerns score from the necessity score. A positive differential implies that the necessity beliefs are stronger than the concerns while a negative differential means that the concerns are stronger than the necessity beliefs. Four attitudinal groups are generated, using the median of the two separate scales: accepting (necessity≥15, concerns<15), ambivalent (necessity≥15, concerns≥15), sceptical (necessity<15, concerns≥15) and indifferent (necessity<15, concerns<15).[37]

Data analysis

Patient characteristics between groups were compared using Student's t-test or χ^2-test (SPSS for Windows version 2.0). Conditional logistic regression was applied to study the effect on dichotomous outcomes (e.g. proportion of satisfied patients, attitudinal groups). Linear regression was used to study the effect on continuous outcomes (e.g. concerns and needs scale). Effect modification was assessed with gender, medication class, age and ethnicity as variables. Effect modification was defined as a significant interaction ($p<0.10$) between group allocation and the variable in question. Gender, age and medication class were studied as potential confounders. Because of the possibility of selection bias, we performed both an intention-to-treat (ITT) analysis and a per-protocol (PP) analysis. In the ITT-analysis we compared all patients in the intervention arm (the 'eligible' patients) whether they received counselling or not with patients who received usual care. In the PP analysis we included only the patients who actually received counselling. Linear and logistic analysis taking clustering within pharmacies into account (by using the *vce* cluster command) was performed using Stata 13.0.

Ethics and confidentiality

The Medical Ethics Review Committee (METC) of the University Medical Centre Utrecht concluded that the Dutch Medical Research Involving Human Subjects Act (WMO) was not applicable. The divisional Institutional Review Board approved the protocol. In order to protect the patients' privacy, all data were coded by the participating pharmacies. The trial was registered at the Dutch trial registry via www.trialregister.nl under the identifier NTR3237.

Results

The overall response rate on the questionnaire was 22.9% (229 patients). 18 questionnaires were excluded because of incompleteness. Of the remaining 211 respondents, 117 belonged to the usual care arms and 94 to the intervention arm ('Eligible' patients) (see Figure 1). Of the 'eligible' patients 60% (56) actually had received counselling and 38 did not. Registered reasons for not providing counselling in the intervention group were: patients refused the counselling (7), patients could not be reached (6) and no telephone number was available (4). For the remaining 21 patients no (clear) reason was registered.

Table 1 shows the baseline characteristics of the responders. The average age of patients who were randomized to the intervention was not significant different from the usual care arm. However, patients in the intervention arm who did not receive the intervention ($n=38$), were younger compared to patients in the usual care arm ($p<0.05$). Moreover, in

the intervention arm the proportion of antidepressant users was higher compared to the usual care arm ($p<0.05$).

Table 1: Socio-demographic and medication characteristics of responding patients.

Characteristic	Usual care arm (n=117)	Intervention arm		
		Eligible patients (ITT) (n=94)	With counselling (PP) (n=56)	No counselling (n=38)
Age, mean (SD), years	62.2 (11.9)	59.9 (13.5)	62.8 (12.1)	**55.7 (14.4)**
Female gender, % (n)	62 (53.0%)	52 (55.3%)	30 (53.6%)	22 (57.9%)
Western ethnicity, % (n)	109 (93.2%)	84 (89.4%)	109 (93.2%)	35 (92.1%)
Respondents per medication class				
RAS-inhibitor	52 (44.4%)	30 (31.9%)	18 (32.1%)	12 (31.6%)
Antilipaemic	36 (30.8%)	30 (31.9%)	17 (30.4%)	13 (34.2%)
Bisphosphonate	16 (13.7%)	10 (10.6%)	8 (14.3%)	2 (5.3%)
Antidepressant	13 (11.1%)	**24 (25.5 %)**	**13 (23.2 %)**	**11 (28.9%)**
Indication according to patient				
RAS-inhibitors primary prevention	36 (69.2%)	23 (76.7%)	15 (83.3%)	8 (66.7%)
Antilipaemic: primary prevention	25 (69.4%)	24 (80.0%)	13 (76.5%)	11 (84.6%)
Bisphosphonate: osteoporosis	9 (56.2%)	6 (60.0%)	4 (50.0%)	2 (100%)
Antidepressant: depression	8 (61.5%)	15 (62.5%)	8 (61.5%)	7 (63.6%)

Data are presented as mean ± Standard Deviation (SD), n (%).

Bold: $p<0.05$ compared to usual care arm.

General satisfaction with counselling

In the usual care arm 31% (33/108) of the patients answered positive on at least one of the questions compared to 47% (40/85) (ITT) and 63% (32/51) (PP) in the intervention arm (see Table 2). In the intervention arm relatively more patients indicated that the pharmacists asked about the experiences, side effects, whether the patient managed to take the medication as prescribed and provided enough personal counselling. Gender was a significant effect modifier and thus we studied the effect of the intervention in women and men separately. In this subgroup analysis the stronger effects of the intervention were mostly attributable to low counselling rates among men in the usual care arm.

Of the patients in the intervention arm, 86% (42/49) said to appreciate this intervention, 74% (34/46) stated that telephone counselling had an added value and 63% (30/48) stated that they would like to be contacted by the pharmacist the next time they start with medication. However, 46% (22/48) preferred face-to-face counselling over telephone counselling. Of the men 88% (21/24) stated that telephone counselling had an added value compared to 59% (13/22) of the women (χ^2-test $p<0.05$).

Table 2: Effect of intervention on patients' general satisfaction with counselling /pharmaceutical care in the first three months.

Question asked: "Did a pharmacist or pharmacy-employee…	Proportion of respondents with positive answer % (n/N)			Adjusted effect size[a] OR (95% CI)	
	Usual care arm	Eligible patients (ITT)	Patients with counselling (PP)	Eligible patients (ITT)	Patients with counselling (PP)
Overall					
… ask you about your experiences with *the medication*?	15.6 (17/109)	32.2 (29/90)	48.1 (26/54)	**2.5 (1.2,5.3)**	**5.5 (2.3,13.3)**
… ask you if you suffered from any side effects?	10.1 (11/109)	29.2 (26/89)	43.4 (23/53)	**3.6 (1.9,6.9)**	**7.4 (3.7,14.7)**
… provide enough personal counselling?	17.6 (19/108)	27.6 (24/87)	40.4 (21/52)	**1.8 (1.1,2.7)**	**3.1 (1.8,5.4)**
… ask you if you manage to take your medication as prescribed?	19.4 (21/108)	34.1 (30/88)	45.3 (24/53)	**2.3 (1.4,3.9)**	**3.8 (1.8,8.0)**
Patient responded positive on at least one item	30.6 (33/108)	47.1 (40/85)	62.7 (32/51)	**2.2 (1.3,3.6)**	**4.2 (1.8,9.8)**
Women					
… ask you about your experiences with *the medication*?	25.4 (15/59)	28.0 (14/50)	50.0 (13/26)	1.2 (0.5,2.8)	**2.9 (1.1,7.2)**
… ask you if you suffered from any side effects?	16.9 (10/59)	26.5 (13/49)	46.2 (12/26)	1.7 (1.0,2.9)	**3.6 (1.8,7.3)**
… provide enough personal counselling?	18.6 (11/59)	18.8 (9/48)	50.0 (13/26)	1.0 (0.4,2.4)	2.1 (0.9,5.2)
… ask you if you manage to take your medication as prescribed?	27.1 (16/59)	30.6 (14/49)	50.0 (13/26)	1.3 (0.7,2.6)	2.2 (0.7,6.7)
Men					
… ask you about your experiences with *the medication*?	4.0 (2/50)	37.5 (15/40)	46.4 (13/28)	**14.6 (3.5,61.7)**	**28.5 (6.2,130)**
… ask you if you suffered from any side effects?	2.0 (1/50)	32.5 (13/40)	40.7 (11/27)	**25.1 (4.3,147)**	**47.6 (8.0,283)**
… provide enough personal counselling?	16.3 (8/49)	38.5 (15/39)	30.8 (8/26)	**3.1 (1.2,7.9)**	**5.2 (1.7,16.1)**
… ask you if you manage to take your medication as prescribed?	10.2 (5/49)	38.5 (15/39)	40.7 (11/27)	**5.4 (1.8,16.4)**	**8.7 (2.6,29.7)**

Bold: $p<0.05$ compared to Usual care arm. [a] Effect size adjusted for age, gender, medication class. Odds ratio (OR) with 95% confidence interval for the difference in outcome values between the intervention arm and usual care arm. The likelihood of experiencing counselling is bigger (OR > 1) or smaller (OR < 1) for participants in the intervention arm compared with participants in the usual care arm.

Table 3: Effect of intervention on patients' satisfaction with information about medicines.

"Please rate the information you have received about each of the following aspects of your medicines."	Proportion patients answering 'about right' % (n/N)			Adjusted effect size OR (95% CI)[a]	
	Usual care arm	Eligible patients (ITT)	Patients with counselling (PP)	Eligible patients (ITT)	Patients with counselling (PP)
Overall					
How long it will take to act	41.5 (44/106)	51.6 (47/91)	55.6 (30/54)	1.3 (0.9,2.0)	**1.6 (1.0,2.6)**
How you can tell if it is working	36.9 (38/103)	41.9 (36/86)	46.0 (23/50)	1.2 (0.9,1.8)	**1.6 (1.1,2.3)**
How long you will need to be on your medicine	30.5 (32/105)	40.0 (34/85)	48.0 (24/50)	1.3 (0.7,2.5)	**2.2 (1.1,4.5)**
How to get a further supply	42.9 (45/105)	53.5 (46/86)	58.0 (29/50)	1.6 (0.9,2.7)	**2.1 (1.3,3.4)**
Whether the medicine has any unwanted effects (side effects)	31.8 (34/107)	38.6 (34/88)	44.2 (23/52)	1.1 (0.8,1.7)	1.6 (1.0,2.5)
What are the risks of you getting side effects	46.2 (48/104)	44.8 (39/87)	49.0 (25/51)	0.9 (0.5,1.5)	1.1 (0.6,2.0)
What you should do if you experience unwanted side effects	42.9 (45/105)	43.2 (38/88)	46.2 (24/52)	0.9 (0.5,1.6)	1.1 (0.6,1.9)
Whether the medicine interferes with other medicines	27.4 (29/106)	34.5 (30/87)	41.2 (21/51)	1.2 (0.7,2.0)	1.8 (0.9,3.5)
What you should do if you forget to take a dose	29.5 (31/105)	34.1 (30/88)	44.2 (23/52)	1.2 (0.7,2.0)	1.8 (0.9,3.4)
Women					
How long it will take to act	49.1 (28/57)	46.0 (23/50)	53.6 (15/28)	0.8 (0.4,1.5)	1.0 (0.4,2.2)
How you can tell if it is working	46.4 (26/56)	34.8 (16/46)	40.0 (10/25)	0.6 (0.3,1.2)	0.8 (0.3,1.8)
How long you will need to be on your medicine	42.1 (24/57)	37.8 (17/45)	48.0 (12/25)	0.8 (0.4,1.4)	1.2 (0.5,2.5)
How to get a further supply	47.4 (27/57)	50.0 (23/46)	56.0 (14/25)	1.0 (0.4,2.5)	1.4 (0.5,4.0)
Whether the medicine has any unwanted effects (side effects)	39.7 (23/58)	27.7 (13/47)	30.8 (8/26)	**0.4 (0.2,0.9)**	0.6 (0.3,1.2)
What are the risks of you getting side effects	58.6 (34/58)	43.5 (20/46)	48.0 (12/25)	**0.5 (0.3,0.9)**	0.6 (0.3,1.2)
What you should do if you experience unwanted side effects	56.1 (32/57)	36.2 (17/47)	38.5 (10/26)	**0.4 (0.2,0.6)**	**0.4 (0.2,0.7)**
Whether the medicine interferes with other medicines	36.2 (21/58)	25.5 (12/47)	30.8 (8/26)	**0.5 (0.3,0.7)**	0.7 (0.3,1.4)
What you should do if you forget to take a dose	36.2 (21/58)	19.1 (9/47)	26.9 (7/26)	**0.3 (0.2,0.6)**	0.5 (0.2,1.1)
Men					
How long it will take to act	32.7 (16/49)	58.5 (24/41)	57.7 (15/26)	**2.9 (1.0,7.9)**	3.3 (0.8,13.1)
How you can tell if it is working	25.5 (12/47)	50.0 (20/40)	52.0 (13/25)	**3.0 (1.4,6.5)**	**4.4 (1.2,16.1)**
How long you will need to be on your medicine	16.7 (8/48)	42.5 (17/40)	48.0 (12/25)	3.3 (0.9,13.0)	**7.5 (1.1,48.9)**
How to get a further supply	37.5 (18/48)	57.5 (23/40)	60.0 (15/25)	**2.6 (1.2,5.7)**	**2.9 (1.1,7.3)**
Whether the medicine has any unwanted effects (side effects)	22.4 (11/49)	51.2 (21/41)	57.7 (15/26)	**3.5 (1.8,6.8)**	**7.0 (4.2,11.6)**
What are the risks of you getting side effects	30.4 (14/46)	46.3 (19/41)	50.0 (13/26)	1.8 (0.8,4.0)	2.4 (0.9,6.5)
What you should do if you experience unwanted side effects	27.1 (13/48)	51.2 (21/41)	53.8 (14/26)	2.8 (0.7,10.5)	**4.7 (1.1,21.3)**
Whether the medicine interferes with other medicines	16.7 (8/48)	45.0 (18/40)	52.0 (13/25)	**4.0 (1.4,11.4)**	**7.9 (1.8,34.9)**
What you should do if you forget to take a dose	21.3 (10/47)	51.2 (21/41)	61.5 (16/26)	**4.0 (1.6,9.6)**	**7.9 (2.8,22.3)**

Bold: p<0.05 compared to Usual care arm. [a]Effect size is the odds ratio (OR) with 95% confidence interval for the difference in outcome values between the intervention arm and usual care arm and is adjusted for gender, medication class and age. Usual care arm is reference category. OR: likelihood of being satisfied with information ('about right') is smaller (OR < 1) or bigger (OR > 1) for participants in the intervention arm compared to participants in the usual care arm.

Satisfaction with information about medicines

In the intention-to-treat analysis there were no statistically significant differences between both arms in the satisfaction with information on medicines (see Table 3). However patients with counselling were more satisfied on four items: “How long it will take to act”, “How you can tell if it is working”, “How long you will need to be on your medicine” and “How to get a further supply”. Also on three other items we found some effect but this was not statistically significant. After stratification for gender, men in the intervention arm were significantly more satisfied on 6 of 9 information items compared to usual care whereas women were less satisfied with information on four items compared to women with usual care. In the PP-analysis this number was 7 respectively 1.

Beliefs about medicines

In the overall study population there was no significant difference in necessity beliefs and concerns between the intervention arm and the usual care arm (see Table 4). In the usual care arm the necessity-concerns differential was -0.35 points which implies that the concerns were 0.35 points higher than the necessity beliefs. Theoretically the differential can range from -20 to +20. For the ‘eligible patients’ this difference was 0.60 and for patients with counselling 1.2 which implies that the necessity beliefs outweighed the concerns. The difference between the differential in the usual care arm and intervention arm was 1.0 (95% CI -1.1, 3.2) (ITT) and 1.7 (95% CI 0.08, 3.2) (PP). This significant effect in patients with counselling was due to a non-significant increase in necessity beliefs (0.5) and a significant decrease in concerns (1.3, 95% CI -2.5, -0.02). As only gender was an effect modifier, the effect was studied for both genders. Men in the intervention arm reported significantly lower concerns compared to men in the usual care arm. For women no differences between both arms were found.

There was no significant difference in distribution of patients over the four attitudinal beliefs groups. In the intervention arm the proportion of sceptical patients (11.0%) is smaller compared to the usual care arm (21.2%) but this is not statistically significant ($p=0.06$, χ^2-test). But after correcting for age, gender and medication class, the likelihood of being ‘sceptical’ was significantly lower in the PP-arm compared to the usual care arm (OR 0.5, 95% CI 0.3, 0.9).

Table 4: Effects of intervention on beliefs about medication.

Measures Beliefs about medicines	Average score[a]			Adjusted effect size (95% CI)[d]	
	Usual care arm	Eligible patients (ITT)	Patients with counselling (PP)	Eligible patients (ITT)	Patients with counselling (PP)
Overall					
BMQ specific necessity[b]	13.1 (3.6)	13.4 (3.9)	13.6 (3.7)	0.6 (-1.2,2.3)	0.5 (-1.5,2.5)
BMQ specific concerns[b]	13.5 (3.6)	12.8 (4.0)	12.4 (3.4)	-0.6 (-1.2,0.1)	**-1.3 (-2.5,-0.0)**
BMQ differential[c]	-0.35 (4.5)	0.60 (4.4)	1.2 (3.9)	1.0 (-1.1,3.2)	**1.7 (0.1,3.2)**
Women					
BMQ specific necessity[b]	12.8 (3.7)	13.0 (4.0)	13.6 (0.36)	0.4 (-1.7,2.5)	0.8 (-2.7,4.2)
BMQ specific concerns[b]	12.6 (3.6)	12.9 (4.4)	12.6 (3.5)	0.5 (-1.1,2.1)	-0.1 (-1.8,2.0)
BMQ differential[c]	0.1 (4.5)	0.1 (4.5)	1.0 (4.3)	0.0 (-2.9,2.3)	0.9 (-2.1,3.9)
Men					
BMQ specific necessity[b]	13.4 (3.5)	14.0 (3.8)	13.6 (3.5)	0.5 (-1.6,2.6)	0.1 (-1.9,2.0)
BMQ specific concerns[b]	14.6 (3.3)	12.8 (3.4)	**12.2 (3.3)**	**-1.8 (-3.4,-0.3)**	**-2.6 (-4.2,-0.9)**
BMQ differential[c]	-0.9 (4.5)	1.2 (4.2)	1.4 (3.6)	2.1 (-0.2,4.4)	2.4 (-0.4,5.2)

Bold: p<0.05 compared to usual care arm. [a] Descriptive data are means (SD). Per patient a score on both the necessity scale and concerns scale are assessed (with a range from 5 to 25). [b] Higher scores indicate stronger necessity beliefs or more concerns. [c] Scores >0 means that necessity beliefs are stronger than concerns beliefs. Score <0 means the opposite. Scores can range from -20 to +20. [d] Effect size is the regression coefficient with 95% confidence interval for the difference in outcome values between the intervention arm and usual care arm. Effect size is adjusted for medication class and age.

Table 5: Effects of intervention on beliefs about medication, expressed as attitudinal groups.

Attitudinal group	Proportion of patients (n)		Adjusted effect size (CI 95%)[a]	
	Usual care arm	Eligible patients (ITT)	Eligible patients (ITT)	Patients with counselling (PP)
Sceptical (necessity<15, concerns≥15)	21.2% (22)	11.0% (9)	0.6 (0.3,1.3)	**0.5 (0.3,0.9)**
Ambivalent (necessity≥15, concerns≥15)	21.2% (22)	26.8% (22)	3.1 (0.8,12.6)	2.3 (0.8,12.0)
Indifferent (necessity<15, concerns<15)	41.3% (43)	45.1% (37)	0.8 (0.6,1.2)	1.0 (0.6,2.1)
Accepting (necessity≥15, concerns<15)	16.3% (17)	17.1% (14)	1.5 (0.6,3.8)	1.6 (0.4,4.3)

Bold: p<0.05 compared to usual care arm. [a] Effect size is the odds ratio (OR) with 95% confidence interval for the difference in outcome values between the intervention arm and usual care arm and is adjusted for gender, medication class and age. Usual care arm is reference category. OR: likelihood of being for example 'sceptical' is smaller (OR < 1) or bigger (OR > 1) for participants in the intervention arm in comparison with participants in the usual care arm.

Discussion and conclusion

Discussion

Patients who received telephone counselling by pharmacists after the start of a new medication therapy were more satisfied with counselling in general compared to patients in the usual care arm. This satisfaction related to all contacts with the pharmacy staff in the first three months after the start. Three quarters of the patients who received telephone counselling believed that this kind of counselling has added value. However in the overall population this did not result in a significant increase in satisfaction with information. Nonetheless patients who received the intervention were more satisfied with some information. We did find a small effect of telephone counselling on medication

beliefs: patients with telephone counselling had less concerns towards their medication and had a more positive necessity-concerns balance. These effects on medication beliefs are in line with an earlier finding that counselling by telephone can increase the necessity-concerns differential.[38]

We found significant effect modification by gender and stratification showed that the intervention had almost no effect in women. On the other hand, in men the intervention had a significant effect on all three outcomes. First, compared to the usual care arm more men in the intervention arm said to have received counselling. Moreover, men in the intervention arm were more frequently satisfied with counselling and with information on medicines. Finally, men who received telephone counselling had less concerns about their medication which resulted in a more positive necessity-concerns balance. Although we corrected the effect sizes for age and medication class, the possibility exists that the differences between men and women are explained by an unmeasured variable. However, plausible explanations exist for the difference of effect in men and women. First of all it can be a practical one: men are likely to visit the pharmacy less frequently and ask someone else to pick up the medication. This might lead to a decreased exposure to usual care in men compared to women. Another explanation can be gender differences in communication style of both the health care provider and the patient. Communication style is important for optimal treatment[39] and male and female physicians in general use different styles.[40,41] In the Netherlands slightly more than half of pharmacists and almost all technicians are female. Especially technicians have an important role in counselling patients during the dispensing process. Gender differences also exist in the patients' needs for information and communication.[42,43] These gender differences might also influence the level of care. The fact that several scores in the usual care group were lower in men compared to women corresponds with both explanations. In addition we asked the patients in the intervention arm about their opinion about this intervention and more men thought it had an added value compared to women. So it is plausible that this service is more suitable for men, however more research is needed to provide more information on this possible gender difference.

A limitation of our study is that the pharmacists failed to register the reasons for not providing counselling for one in four patients. A likely explanation for this 'failure' is that the selection for the intervention had to be run weekly and in some weeks this selection has not been made, for example due to vacation or illness of the responsible pharmacist. According to the protocol the call had to be made 7 to 21 days after the first prescription so, if a pharmacist was not able to call the patient within this time window, some patients were missed. The selection of patients for the questionnaire was run independently of the fact that patients were actually called. Therefore it is likely that patients were not selected

for the intervention but were selected for the questionnaire. Since pharmacists did register patient related reasons for not calling we believe that the reasons for not registering were probably not patient related but of an organizational nature. To eliminate all risks of bias we decided to include these patients in the intention to treat analysis. Comparing the results of the ITT and the PP-analysis, the results were in line with the expectation that the effects of the intervention are stronger in the PP-analysis than in the ITT-analysis. Another limitation is the low overall response rate of 22.9%. Our sample size was based on an expected response rate of 30% and we did not take any effect modification into account which leaves our study possibly underpowered. Moreover, we were not able to present the results on adherence yet. These are expected to become available late 2015.

A major strength of this study is that it was implemented in routine care with four different medication classes. The fact that pharmacists were able to include more than half of the patients and perform the intervention in 'daily practice' suggests that it is feasible to implement this intervention in routine care. The quality of the intervention depends on the skills of the pharmacist. To assure treatment integrity we provided training to the pharmacists, an interview protocol and the pharmacists had to register the content of all the calls. The nine participating pharmacies where located both in rural and urban areas of the Netherlands which improves the external validity. Also positive is that the intervention focusses on patients starting treatment regardless if they return for a refill or not. This is relevant since a substantial part of the patients discontinue therapy in the first weeks after the start and will not return to the pharmacy for a refill.[44] This suggests that the intervention can be implemented in a broad range of settings for different types of medication classes.

Conclusions

Counselling by telephone by pharmacists at the start of therapy improves the general satisfaction with counselling. Most patients appreciate this type of counselling and it seems feasible to implement this intervention in daily clinical practice. In the overall study population telephone counselling has no distinct effect on satisfaction with information and on beliefs about medicines. However, patients who received counselling were more satisfied with some information, had less concerns about medication and less frequently had a 'sceptical' attitude. The effects of the intervention were more pronounced in men.

Practice implications

The results of this study suggest that counselling by telephone at the start of therapy improves the satisfaction with counselling by pharmacists. In men telephone counselling

also improves satisfaction with information and reduces the concerns about medication. The difference in effect between men and women suggests that additional counselling will not benefit all patients. Pharmacists should find strategies to direct this intervention to patients who are most likely to benefit. Attention should be paid how to reach more patients although the intervention is relatively easy to implement.

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Appendix

Table 6: Satisfaction with Information about Medicines Scale (SIMS) questions.

Please rate the information you have received about each of the following aspects of your medicines.		Included
1.	What your medicine is called	
2.	What your medicine is for	
3.	What it does	
4.	How it works	
5.	How long it will take to act	Yes
6.	How you can tell if it is working	Yes
7.	How long you will need to be on your medicine	Yes
8.	How to use your medicine	
9.	How to get a further supply	Yes
10.	Whether the medicine has any unwanted effects (side effects)	Yes
11.	What are the risks of you getting side effects	Yes
12.	What you should do if you experience unwanted side effects	Yes
13.	Whether you can drink alcohol whilst taking this medicine	
14.	Whether the medicine interferes with other medicines	Yes
15.	Whether the medication will make you feel drowsy	
16.	Whether the medication will affect your sex life	
17.	What you should do if you forget to take a dose	Yes

Item 1 to 9: Action and usage scale. Item 10 to 17: Potential problems of medication subscale.

CHAPTER 4.5

Improving medication adherence using a Telephone Counselling Intervention by Pharmacists (TelCIP): a pragmatic cluster randomized trial

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Abstract

Objectives: To assess the effect of a pharmacist telephone counselling intervention on patients' medication adherence.

Design: Pragmatic cluster randomized controlled trial.

Setting: 53 Community pharmacies in The Netherlands.

Participants: Patients initiating treatment with antidepressants, bisphosphonates, Renin-Angiotensin System (RAS)-inhibitors or statins were included when ≥18 years and responsible for their medication taking. Pharmacies in arm A provided the intervention for the first two classes and pharmacies in arm B for the latter two.

Intervention: Intervention was a telephone counselling intervention by pharmacist (TelCIP) 7-21 days after the start of therapy. Counselling included assessment of practical and perceptual barriers and provision of information and motivation.

Main outcome measure: Primary outcome was refill adherence measured over 1 year expressed as continuous outcome and dichotomous (refill rate≥80%). Secondary outcome was discontinuation within one year.

Results: In the control arms 3,627 patients were eligible and 3,094 in the intervention arms. Of the latter, 1,054 patients (34%) received the intervention and 1,495 (49%) patients were not registered. Overall mean adherence rates between intervention and usual care arm were not significantly different (74.7% resp. 74.5%). More patients starting with RAS-inhibitors were adherent in the intervention arm compared to usual care (81.4% versus 74.9% with odds ratio (OR) 1.43, 95%CI 1.11-1.99). No significant differences were found for the other three classes in the intention to treat analyses. Comparing patients with counselling to patients in the usual care arm (per protocol analysis), more patients were adherent in the adjusted model (OR 1.48, 95% CI 1.20-1.78) and in patients starting with RAS-inhibitors, statins and bisphosphonates.

Conclusions: Telephone counselling at start of therapy had no overall effect on adherence nor for participants starting with antidepressants. However it statistically significant improved adherence to RAS-inhibitors and suggested also a positive effect on adherence to lipid lowering drugs and bisphosphonates.

Introduction

Adherence to medication is a primary determinant of treatment success, and it is often suboptimal.[1] The WHO definition of adherence to medication is *"the extent to which a person's behaviour (taking medication), corresponds with agreed recommendations from a health care provider".*[1] Practical and perceptual barriers can prevent patients from adhering to the prescribed regimen. Practical barriers relate to cognition and self-efficacy whereas perceptual barriers relate to beliefs about the necessity and drawbacks of drug treatment.[2] Health care providers (HCP) including pharmacists can reduce these barriers and thereby promote adherence.[3-5] Pharmacists have frequent interactions with patients, are easy accessible, well trained and educated. Guidelines recommend counselling by pharmacists to improve medication adherence, especially at the start of therapy.[3,4,6-8] At the first dispensing of a new drug, patients should receive written and oral information including instructions for use. At the first refill, counselling should focus on exploring patients' experiences with the medication. However, in daily practice guidelines are often not followed[6,9,10] resulting in suboptimal counselling.[11-13] The reasons for deviating from guidelines by pharmacists can be patient related (e.g. the patient is unable to visit the pharmacy, there are language problems, or the patient has low health literacy skills). Reasons can also be pharmacy or health system related (e.g. the pharmacy is understaffed, there is no priority for counselling, there is a lack of privacy or lack of remuneration). Telephone counselling may be a feasible alternative for face-to-face counselling.[14,15] It has several advantages: first of all the patient can be in or move to a safe environment and (lack) of privacy is not an issue. Moreover patients who are not able to visit the pharmacy can be reached. Also, pharmacists can prepare themselves on the call and the telephone calls can be planned (if necessary outside office hours). To test the effect of counselling by telephone on adherence, we designed a cluster randomized trial. Primary goal of this study was to assess the effect of a pharmacist telephone counselling intervention on patients' medication adherence.

Methods

Study design

The protocol for this multicentre, community pharmacy based, cluster randomized controlled trial (the TelCIP trial) has been described elsewhere.[16] Pharmacies were randomized in two arms. Patients in arm A starting with antidepressants or bisphosphonates and patients in arm B starting with RAS-inhibitors or statins received the intervention. Patients in arm A starting with RAS-inhibitors or statins and patients in arm B starting with antidepressants or bisphosphonates received usual care (see Figure 1).

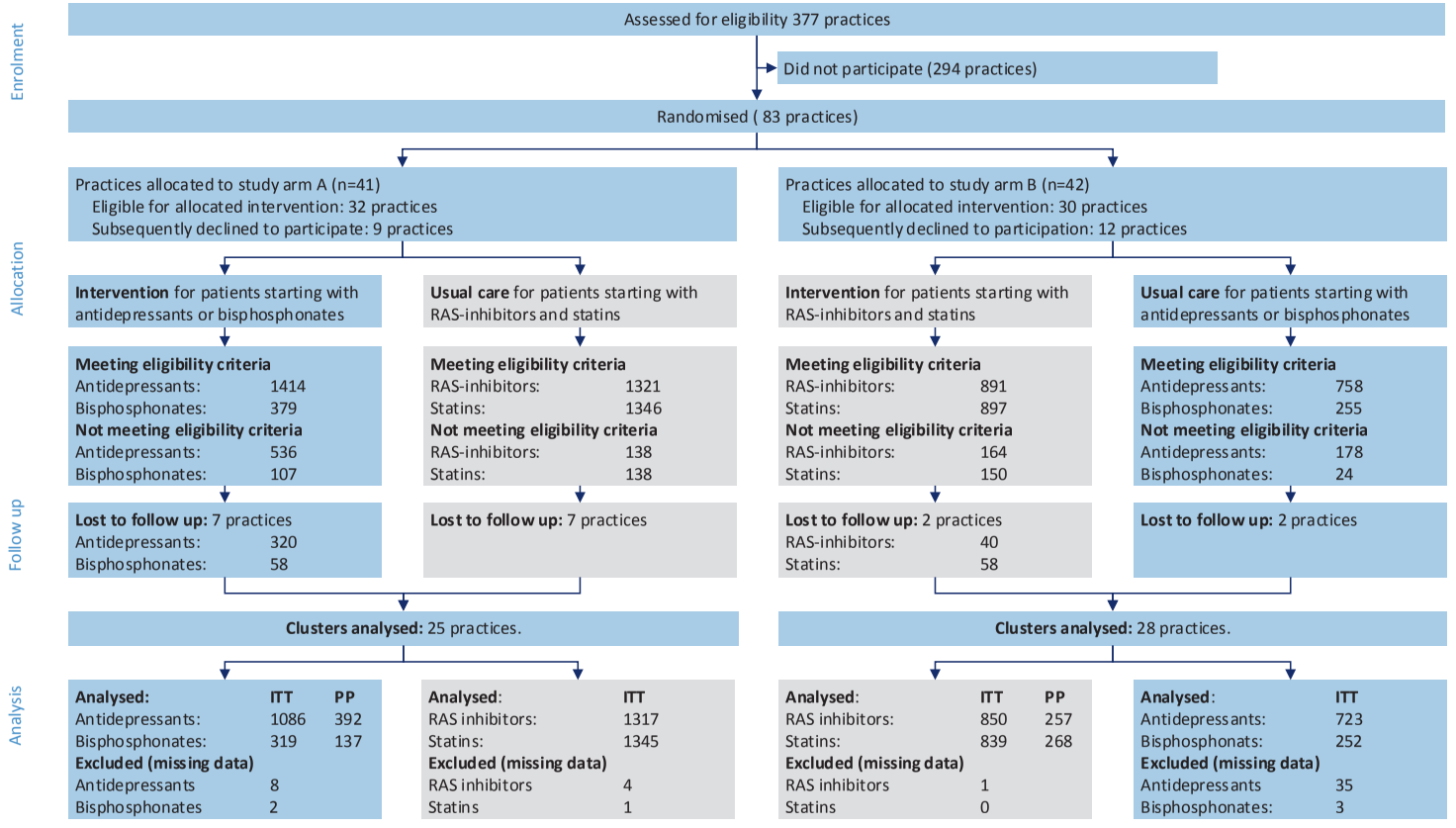

Figure 1: Practice and patients flowchart. This figure outlines the progress of clusters (pharmacies) and individual patients through the phases of the trial. Numbers are patients unless stated otherwise.

Participants

Pharmacies

The study was conducted in community pharmacies in the Netherlands, both in rural and urban areas. Within every pharmacy one dedicated staff member was assigned to perform the intervention. This could be the pharmacist, but also a non-pharmacist employee with a bachelor degree (B), pharmacist trainee (BPharm) or pharmacy technician. In this paper we used the term pharmacist to describe all these staff members unless stated otherwise. The term pharmacy practitioner was used for bachelors and trainees. Pharmacists received a three hour training aimed at understanding beliefs and behaviour of patients related to medication intake. The training included case studies and an assessment of the level of theoretical knowledge on communication.[16] Pharmacist trainees did not receive additional training since communication is a central subject in the curriculum.[17,18] All pharmacies received a study manual.

Patients

Inclusion criteria were:

- Aged ≥ 18 years
- Responsible for own drug intake
- Speaking Dutch or same language as pharmacist/pharmacy worker
- Initiating one of the medication classes described above[16]. "Initiating" was defined as receiving a prescription within the medication class for the first time in 12 months

Patients were excluded if the medication was prescribed for a short-term indication (e.g. antidepressant for smoking cessation or sleeping disorders) or had a severe mental illness. Patients were recruited between October 2010 and March 2013.

Procedure

Usual care

The control group received usual pharmaceutical care. Usual care in Dutch pharmacies should consist of providing the patient with written and oral information at the start of pharmacotherapy. In practice this is mostly done by a pharmacy technician. The first dispensing provides medication for a maximum of two weeks. Guidelines recommend that at the first refill, patients are asked about their experiences with the medication. If necessary, additional information or counselling should be provided.

Intervention arm

Patients in the intervention arms were selected weekly through an automated selection procedure. Subsequently the pharmacist contacted patients by telephone between 7 to 21 days after the first prescription. Main goal of this call was to improve adherence. The call was supported by a pre-tested interview protocol aimed at addressing the following subjects: (1) need for information; (2) actual medication intake behaviour; (3) practical barriers including side effects; (4) perceptual barriers including concerns or low necessity beliefs. The protocol was medication class specific and items like specific side effects and intake advices were included. A general interview protocol has been published elsewhere, together with the study protocol.[16]

Data collection

Starting in March 2014, one year after inclusion of the last patient, pharmacy dispensing data were collected. These data included all prescriptions from 12 months before the start of the intervention until extraction date. Pharmacy dispensing records included dispensing date, quantity dispensed, prescribed daily dose and information about the prescriber. All patient data were anonymised at the pharmacies.

Outcome measures

The primary outcome was refill adherence (Medication Possession Ratio modified, MPRm)[19] in the year following start of medication therapy, and was expressed both as a continuous and as a dichotomous measure; patients with an MPRm≥80% were considered as adherent and those with an MPRm<80% as non-adherent. The MPRm was calculated by dividing the total number of days' supply of a drug, excluding the last supply, by the number of days between the first and the last dispensing or first discontinuation date within the year after the start, whichever came first. This value was multiplied by 100 to provide a refill adherence percent value. The number of days supplied was calculated by dividing quantity dispensed by the prescribed daily dose. In case of missing dosing instructions, the instruction of the previous dispensing or the next dispensing (in case of a first prescription) was used. Retrospective compensation was not allowed and any stock was only allowed to fill the first following gap.

Secondary outcome was persistence, which was expressed as the time from initiation until discontinuation. Discontinuation was defined as exceeding a gap of 90 days with no medication available within the one-year observation period.

Treatment fidelity

Treatment fidelity was promoted through the design of the study, by providing training to pharmacists, by providing a manual, an interview protocol and an online self-report.[20] Assessment of treatment fidelity in this study will be submitted for publication. The self-report contained all items from the interview protocol and was used for continuously monitoring of implementation and for assessment of treatment fidelity. The pharmacists registered information on duration of the calls and number of attempts as well as the topics discussed and additional interventions performed. Reasons for not including a selected patient were also registered (see Appendix 1 of Chapter 4.2).

Sample size

Sample size calculation was based on the primary outcome, the proportion of adherent patients (MPRm≥80%), using a type one error (α) for a two sided test of 0.05 and a power of 0.80 (1-β). To demonstrate an improvement of the proportion of adherent patients from 70% to 80%, an individually randomized trial would need 294 patients per arm and per medication class.[21] Correcting for clustering effects using an intracluster (or intraclass) correlation coefficient (ICC) of 0.02 resulted in the necessity to include at least 15 pharmacies with at least 30 patients each.[16,21-24]

Practice randomization and data analysis

The pharmacies were randomly allocated to either study arm A or study arm group B (Figure 1) in a 1:1 ratio. The primary analysis was based on the intention to treat (ITT) principle and the four medication classes were pre-defined subgroups. In a secondary, per protocol (PP) analysis, we compared patients in the intervention arm who actually received counselling, to patients in the usual care arm. Effect analyses were performed by a statistician (SB) blinded to the group allocation. Linear mixed-effects models were used for continuous outcomes and generalized mixed-effect models with the logit link function were used for dichotomous outcomes, both with pharmacy as random effect and percentile bootstrap confidence intervals with 1,000 replications. Discontinuation in the first year was assessed using the Cox proportional hazards frailty model with the pharmacy as a random frailty factor. We considered a p-value of less than 0.05 to be statistically significant. For the descriptive and effect analyses we used R software version 3.1.2. (Austria, www.R-project.org). For multilevel analysis, library 'lme4' was used with 'lmer' for continuous outcomes, 'glmer' for dichotomous outcomes and 'survival' for Cox regression. In a secondary, exploratory analysis we tested several factors as potential modifying factors: age, gender, Chronic Disease Score (CDS), and the status score at baseline. The CDS uses medication dispensed, as a surrogate marker for chronic illness.[25]

The status score (SS) is used as a marker for the individual socioeconomic status (SES). The SS is based on the patient's postal code and uses the average income, income, education and employment of persons living in that area.[26]

Ethics and confidentiality

The Medical Ethics Review Committee (METC) of the University Medical Centre Utrecht has considered our research proposal in a meeting on 13 July 2010 and concluded that the Dutch Medical Research Involving Human Subjects Act (WMO) was not applicable. Consequently the protocol was submitted to the Institutional Review Board (IRB) of UPPER, Utrecht University which approved the study protocol. The trial was registered at www.trialregister.nl under the identifier NTR3237. Patients received an information letter and gave informed consent before participating.

Results

Of 62 pharmacies that included patients in the study, dispensing data were available from 53 pharmacies (25 arm A and 28 arm B) (see Figure 1). In total 6,731 patients were eligible (3,627 control patients and 3,094 intervention patients). A telephone call was registered for 1,054 (34%) of the 3,094 patients in the intervention arm. For 545 (18%) patients it was registered that the patient did not receive the counselling intervention and for 1,495 (48%) patients no registration was found.

Baseline characteristics are presented in Table 1. Overall, patients in the intervention arm were younger and more often female. However this was mainly due to the slight unequal distribution of medication classes over both arms. In the supplementary tables additional information is provided: health characteristics are presented in Table 3, information at cluster level in Table 4 and on eligible patients without counselling in Table 5.

In a secondary analysis we compared baseline characteristics for patients with counselling (PP) to patients in the usual care arm. Patients with counselling starting with RAS-inhibitors (p=0.049) or statins (p=0.04) where slightly older compared to patients with usual care. Other characteristics were not significantly different.

The most important reasons for not delivering the intervention where: no telephone number available (186, 32%), patient could not be reached (185, 31%), not interested (83, 14%), refused cooperation (44, 7%). On average the call lasted 8.3 minutes (Standard Deviation (SD) 4.4) and the preparation time for each call was 6.2 minutes (4.7). The pharmacists (PharmD) were responsible for 36% of the calls, pharmacy practitioners for 43% and technicians for 17%. In 79.5% of the calls all five knowledge items were reported to be discussed. These items included knowledge about reason of use (indication),

mechanism of action, duration of treatment, correct moment of intake and possible side effects.

Doubts about necessity were discussed in 93.1% of the calls, concerns about side effects in 91.5% and experiences with side effects in 94.8%. According to the pharmacists 31.0% of the patients experienced side effects. In patients starting with antidepressants this proportion was higher compared to other medication classes (χ^2-test p<0.005).

Table 1: Baseline socio-demographic and health characteristics for each group at individual level.

Characteristic	Usual Care	Eligible patients (ITT)	Patients with counselling (PP)
Overall	n=3637	n=3094	n=1054
Mean (SD) age, years	59.0 (15.1)	56.9 (15.9)	58.6 (15.8)
Female, n (%)	1987 (54.6)	1785 (57.7)	644 (61.1)
Mean (SD) status score	-0.44 (1.29)	-0.31 (1.20)	-0.43 (1.27)
Mean (SD) CDS	3.3 (3.1)	3.1 (3.1)	3.4 (3.2)
Patients starting with RAS-inhibitor	n=1317	n=850	n=257
Mean (SD) age, years	61.1 (13.7)	62.2 (13.0)	63.8 (12.2)
Female, n (%)	710 (53.9)	439 (51.6)	145 (56.4)
Mean (SD) status score	-0.62 (1.32)	-0.01 (1.06)	-0.08 (1.18)
Mean (SD) CDS	3.3 (3.1)	3.3 (3.0)	3.5 (2.9)
Patients starting with statin	n=1345	n=839	n=268
Mean (SD) age, years	60.6 (12.6)	61.6 (11.5)	62.5 (11.3)
Female, n (%)	660 (49.1)	414 (49.3)	139 (51.9)
Mean (SD) status score	-0.60 (1.29)	-0.02 (0.97)	-0.01 (0.98)
Mean (SD) CDS	3.4 (2.9)	3.4 (2.8)	3.6 (2.8)
Patients starting with bisphosphonate	n=252	n=319	n=137
Mean (SD) age, years	66.5 (13.4)	66.2 (13.5)	67.8 (12.1)
Female, n (%)	186 (73.8)	251 (78.7)	111 (81.0)
Mean (SD) status score	0.14 (1.12)	-0.54 (1.25)	-0.64 (1.23)
Mean (SD) CDS	4.8 (3.9)	5.1 (3.7)	5.4 (3.7)
Patients starting with antidepressant	n=723	n=1086	n=392
Mean (SD) age, years	49.4 (17.9)	46.5 (16.1)	49.3 (17.0)
Female	431 (59.6)	681 (62.7)	249 (63.5)
Mean (SD) status score	-0.03 (1.15)	-0.70 (1.33)	-0.89 (1.34)
Mean (SD) CDS	2.3 (2.9)	2.2 (2.9)	2.4 (3.1)

Values at are numbers (percentages) unless stated otherwise.

Primary outcome measures

Overall

In the overall ITT analysis we found a mean adherence rate (MPRm) of 74.7% (SD 37.5) for intervention patients and 74.5% (SD 37.9) for control patients (see Table 2). The proportion adherent patients (MPRm≥80%) was 69.0% in the intervention arm and 69.9% in the usual care arm and differences between intervention and usual care arms were not

significantly different on both outcomes. Adjusting for medication class, age, status score, CDS and gender the proportion adherent patients was not significantly different in both arms (Adjusted odds ratio [OR] 1.10, 95% CI 0.94, 1.25). Patients with counselling (PP-analysis) were not significantly more adherent (78.5% resp. 74.3%, see Table 2). However the adjusted model demonstrated statistically significant more adherent patients in the intervention arm with an odds ratio of 1.48 (95% CI 1.20, 1.78).

Effect per medication class

The mean adherence rate in patients in the intervention arm starting with RAS-inhibitors was 84.1% (SD 31.6) compared to 78.5% (SD 36.6) in the usual care arm which is a significant improvement with a adherence difference based on mixed-effect models of 5.16% (95% CI 1.17, 10.03) (See Table 2). In the intervention arm more patients were adherent (MPRm≥80%) compared to the usual care arm (81.4% versus 74.9% with OR 1.43, 95% CI 1.11, 1.99). Effects on both outcomes were stronger and statistically significant for patients with counselling (PP-analysis). Based on the PP-analysis 16 patients need to be called in order for one extra patient to be adherent (NNT).

In statin users, patients in the intervention arm had a mean adherence rate of 80.5% (32.4) compared to 75.1% (36.8) in the usual care arm, which is a non-significant adherence difference of 4.08% (95% CI -0.81, 6.62). The proportion adherent patients in the intervention arm (75.1%) was not significantly different from the proportion in the usual care arm (68.9%) (OR 1.27, 95% CI 0.86, 1.54). Effects on both outcomes for patients with counselling (PP-analysis) were stronger and statistically significant. The number needed to call is 14.

In patients starting with bisphosphonates, the mean adherence rate in intervention arm (75.2%) was not different from the usual care arm (73.3%) neither was the proportion of adherent patients (70.2% resp. 67.1%). In the PP-analysis we found a significant improvement of adherence in patients with counselling and also in the proportion of adherent patients (MRPm≥80%) and the number needed to call is 11.

For antidepressants we found no significant difference in adherence rate between patients in the intervention arm (62.7% SD 41.7) and patients with usual care (66.8%, 40.9). The proportion adherent patients was also not significantly different between the arms (54.1% resp. 60.4% with OR 0.78, 95% CI 0.59, 1.02). In the PP-analysis we found no significant difference between arms.

Table 2: Effect of telephone counselling on adherence expressed as mean adherence rate, proportion of adherent patients and discontinuation.

Variable	Usual care	Intervention arm (ITT)	Patients with counselling (PP)	ITT-analysis Effect size* (95% CI)	PP-analysis Effect size* (95% CI)
Overall	n=3637	n=3094	n=1054		
Mean adherence (SD)	74.5 (37.9)	74.7 (37.5)	78.5 (35.4)	-1.07 (-8.13,4.15)	3.96 (-2.34,10.3)
Adherence ≥80%, % (n)	69.9 (2,519)	69.0 (2,134)	74.3 (783)	0.92 (0.68,1.27)	1.30 (0.93,2.00)
Discontinued, % (n)	33.2 (1,208)	34.6 (1,069)	33.4 (352)	1.08 (0.82,1.37)	0.96 (0.70,1.21)
RAS-inhibitor users	n=1317	n=850	n=257		
Mean adherence (SD)	78.5 (36.6)	84.1 (31.6)	87.6 (26.4)	**5.16 (1.17,10.03)**	**8.44 (2.01,13.4)**
Adherence ≥80%, % (n)	74.9 (987)	81.4 (692)	84.1 (216)	**1.43 (1.11,1.99)**	**1.71 (1.11,2.62)**
Discontinued, % (n)	27.9 (367)	22.6 (192)	21.8 (56)	**0.77 (0.69,0.91)**	0.73 (0.56,1.02)
Statin users	n=1345	n=839	n=268		
Mean adherence (SD)	75.1 (36.8)	80.5 (32.4)	85.2 (29.0)	4.08 (-0.81,6.62)	**8.97 (3.51,12.1)**
Adherence ≥80%, % (n)	68.9 (926)	75.1 (630)	81.3 (218)	1.27 (0.86,1.54)	**1.83 (1.16,2.49)**
Discontinued, % (n)	32.2 (433)	28.4 (238)	28.0 (75)	0.87 (0.73,1.10)	0.82 (0.65,1.15)
Bisphosphonate users	n=252)	n=319	n=137		
Mean adherence (SD)	73.3 (38.1)	75.2 (38.4)	84.3 (31.7)	-0.54 (-9.43,6.14)	**10.2 (1.98,16.4)**
Adherence ≥80%, % (n)	67.1 (169)	70.2 (224)	81.8 (112)	1.00 (0.57,1.49)	**2.15 (1.32,3.57)**
Discontinued, % (n)	39.3 (99)	38.6 (123)	32.9 (45)	1.00 (0.80,1.40)	0.79 (0.57,1.25)
Antidepressant users	n=723	n=1086	n=392		
Mean adherence (SD)	66.8 (40.9)	62.7 (41.7)	65.8 (41.7)	-3.78 (-8.15,0.93)	-0.55 (-6.04,6.47)
Adherence ≥80%, % (n)	60.4 (437)	54.1 (588)	60.5 (237)	0.78 (0.59,1.02)	1.05 (0.78,1.58)
Discontinued, % (n)	42.7 (309)	47.5 (516)	44.9 (176)	**1.17 (1.01,1.37)**	1.04 (0.84,1.27)

* For 'Mean adherence' the effect size is the 'risk difference' and for proportion of for 'Adherence ≥80%', it is the Odds Ratio. The likelihood of being adherent is bigger (OR > 1) or smaller (OR < 1) for participants in the intervention arm compared with participants in the usual care arm. For discontinuation the effect size is the hazard ratio and the hazard of discontinuing in the first year is bigger (HR>1) or smaller (HR<1) for participants in the intervention arm, compared with participants in the usual care arm. All presented CI's are bootstrap CI's. Abbreviations: ITT, intention-to-treat; PP, per protocol; RAS, renin angiotensin system; CI, confidence interval, NNT, number needed to treat.
Bold: ES is outside 95% CI.

Secondary outcome measures

In the overall population we found no significant effect of the intervention on discontinuation in the first year after initiation (see Table 2). Also in the crude PP-analysis no statistically significant difference was found but in the adjusted model discontinuation was lower (hazard ratio [HR] 0.87, 95% CI 0.80, 0.95). For patients starting with RAS-inhibitors 22.6% of the patients in the intervention arm discontinued therapy compared to 27.9% of patients with usual care which is significantly lower (HR 0.77, 95% CI 0.69, 0.91). The result of the PP-analysis is comparable but not statistically significant. For statins and bisphosphonate users, discontinuation rates were not significantly different (HR 0.87, 95% CI 0.73, 1.10) resp. 0.73, 95% CI 0.56, 1.02).

For patients starting with antidepressants in the intervention arm 47.5% discontinued compared to 42.7% in the usual care arm which is a significant different (HR 1.17, 95% CI 1.01, 1.37). Interestingly in the PP-analysis 44.9% discontinued in the intervention arm which is not significantly different from usual care (HR 1.04, 95% CI 0.84, 1.27).

Discussion

The aim of this study was to assess the effect of telephone counselling at start of therapy on adherence to RAS-inhibitors, statins, bisphosphonates and antidepressants. Overall, no effect of the intervention was found. Results show that adherence was improved for patients starting with RAS-inhibitors. For patients starting with statins or bisphosphonates adherence was only significant improved when comparing patients that received counselling with patients receiving only usual care (PP-analysis). For antidepressants no significant effect was found. The risk of discontinuing with RAS-inhibitors was reduced by the intervention.

Our study has some strengths and limitations. Strength of our study is that it was implemented in a real-life setting and with four different medication classes. The pragmatic design of the trial contributes to the generalizability of the results. Another strength is that a relatively high proportion of eligible patients received the intervention. This is high compared to what is known from literature.[6,10,27,28] For example a study by Van Gompel et al. demonstrated that only 19% of patients starting with a statin received counselling at the start of therapy.[10] Strength is also that the intervention focused on patients starting with treatment, an important phase for patients to accept or reject the therapy. Moreover this intervention includes patients irrespective if they return for a refill or not. So also patients who decided not to initiate or to discontinue were approached. This is relevant since a substantial part of the patients discontinue therapy in the first weeks. Patients not capable of visiting the pharmacy were also included. For the primary analysis the statistician was blinded for group allocation and performed a multilevel

analysis with bootstrap confidence intervals. The participating pharmacies were located in different areas of the Netherlands, both in rural and urban areas and in areas with low and high status scores. Different strategies were used to enhance treatment fidelity for example by preventing contamination using a cluster design, providing standardized training, providing medication class specific interview protocols and treatment manual, and the obligation for pharmacists to complete a self-report questionnaire for every selected patient. Moreover pharmacies received biweekly updates of the number of patients included with benchmark information. The intervention was based on theoretical models and guidelines and the interview protocol contained pre-defined questions and relevant knowledge items. Moreover the protocol stimulated pharmacists to ask about patient opinions, for example by asking "What do you think of getting this medicine?" and to tailor counselling to patients' needs which is important to improve adherence.[29] Our study also has its limitations. Based on the prescription data, more patients should have received the intervention than were registered. The exact reason is not known but possible explanations can be that 1) the computer program did not select all patients, 2) the pharmacist did not run the program or temporarily stopped including patients, 3) the pharmacist did call the patient, but failed to register it and 4) the pharmacist decided not to call the patient for unknown reasons. During interviews with some pharmacists they indicated to have (temporarily) stopped including patients due to staffing problems. Baseline characteristics of non-registered patients were not different from patients with counselling. However to prevent bias, we included all eligible patients based on the prescription data in the ITT analysis which diluted the potential effect of the intervention. In line with the expectations, effects in the PP-analysis were stronger for most outcomes. Another limitation is that we did not included the pre-specified number of patients per medication class however we were able to increase the power by increasing the number of pharmacies.

The lack of improvement of adherence to antidepressant therapy is in line with other published studies.[30] In a review of interventions focussing on antidepressants[31] authors suggest that educational intervention alone is not enough and that complex interventions are needed. However, a recent review indicated that pharmacist care can improve adherence to antidepressants.[32] It was not clear for all trials if the included patients were already on treatment or were initiating treatment. Moreover in all included studies, the patients had an established diagnosis of depression. This is missing in our study and it is unknown if the medication was prescribed for depression or other indications like anxiety disorders. Based on the dispensing data however we know that less than 20% of the patients received a prescription from a psychiatrist in the 12 months before the start of the antidepressant. Our study showed that patients using antidepressants were more

likely to experience side effects. This may have been an additional barrier to improve adherence. Moreover the counselling might have helped patients to make a thought-out decision whether or not to continue treatment, although the effect on adherence might be the same,[33] Studies for other medication classes like antidiabetics,[34,35] antiplatelet medication[36] and statins[37] showed a positive effect of counselling on adherence or clinical outcomes. In literature we found no trials with a comparable intervention studied for antihypertensives. In a trial focussing on bisphosphonates no statistically significant improvement of adherence was found using a telephone motivational interviewing intervention,[38]

Mean adherence rates and proportion of adherent patients were relatively high in our study population, both in the intervention as in the usual care arm. One explanation might be that participating pharmacies are among the best practices that have already implemented counselling guidelines to a large extent. Comparison of adherence data should, however, be performed with caution as the calculated refill-rate is influenced by the method of calculation and assumptions made.[19]

Research demonstrated that adherence to medication is low,[1,39,40] that patients need more information about medication[4,41-43] and that health care providers, including pharmacists, do not regularly discuss medication taking behaviour.[6,10,27] A previous analysis showed that telephone counselling at the start of therapy increased satisfaction with information and increased satisfaction with counselling.[33] This study demonstrated that this intervention also improved medication adherence for some medication classes and that this intervention can be used in pharmacy practice.

Patients have different needs and variability between health care providers in the care they provide exists. More research is needed to identify for which patients and in which setting standard care is sufficient and for which patients standard care is not sufficient and thus need additional counselling for example by telephone. Moreover the cost-effectiveness of the intervention needs to be assessed.

Conclusion

Our study demonstrated that telephone counselling at start of therapy did not affect adherence to antidepressants however it statistically significant improved adherence to RAS-inhibitors and suggested also a positive effect on adherence to lipid lowering drugs and bisphosphonates.

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Supplementary tables

Table 3: Baseline health characteristics for each group at patient level.

Characteristic	Usual Care	Eligible patients (ITT)	Patients with counselling (PP)	Overall
Patients starting with RAS-inhibitor	n=1317	n=850	n=257	n=2167
Use of medication preceding index date:				
Antidiabetics (A10)	176 (13.3)	96 (11.2)	36 (14.0)	272 (12.6)
Antithrombotics (B01)	295 (22.3)	227 (26.7)	67 (26.1)	522 (24.1)
Antihypertensives	604 (46.8)	438 (52.5)	134 (53.0)	1042 (49.1)
Patients starting with statin	n=1345	n=839	n=268	n=2184
Use of medication preceding index date:				
Antidiabetics (A10)	246 (18.3)	128 (15.3)	34 (12.7)	374 (17.1)
Antithrombotics (B01)	425 (31.6)	279 (33.3)	79 (29.5)	704 (32.2)
Antihypertensives	526 (39.3)	369 (44.5)	126 (47.5)	895 (41.3)
Visit to cardiologist or internist in 12 months before index	465 (34.6)	280 (33.3)	90 (33.6)	745 (34.1)
Patients starting with bisphosphonate	n=252	n=319	n=137	n=571
Use of medication preceding index date:				
Calcium suppletion (A12A)	123 (48.8)	163 (51.1)	68 (49.6)	286 (50.1)
Predniso(lo)ne (H02AB06 or H02AB07)	68 (27.0)	85 (26.6)	38 (27.7)	153 (26.8)
Vitamin D (A11CC05)	115 (45.6)	155 (48.6)	67 (48.9)	270 (47.3)
Visit to internist in 12 months before index	248 (98.4)	298 (93.4)	132 (96.4)	546 (95.6)
Patients starting with antidepressant	n=723	n=1086	n=392	n=1809
Use of medication preceding index date:				
Antipsychotic (N05)	47 (6.5)	53 (4.9)	12 (3.1)	100 (5.5)
Benzodiazepin (N05BA, N05CD or N05CF)	250 (34.6)	307 (28.3)	109 (27.9)	557 (30.8)
Visit to psychiatrist in 12 months before index	141 (19.5)	276 (25.4)	99 (25.3)	417 (23.1)

Values are means (standard deviation) unless stated otherwise.
Antihypertensives: Antihypertensives (C02)+ Diuretics (C03) + Beta blocking agents (BBA, C07)+ Calcium channel blockers (CCB, C08)+ RAS inhibitors (C09)).

Table 4: Baseline socio-demographic and health characteristics for each group at cluster level.

Characteristic	Usual Care	Eligible patients (ITT)	Patients with counselling (PP)	Overall
Gender (No/cluster)				
Female	38.2 (34.3)	34.3 (41.2)	12.6 (17.6)	72.5 (85.7)
Male	31.7 (44.1)	25.2 (30.6)	8.0 (10.0)	56.9 (64.0)
Pharmacy inclusion phase				
Phase 1	113.9 (102.5)	95.2 (76.3)	33.4 (29.8)	209.2 (158.3)
Phase 2	14.5 (14.4)	14.4 (13.7)	3.8 (2.8)	28.9 (24.4)
Age groups (No/cluster)				
18-50	19.7 (22.5)	20.3 (28.2)	6.4 (11.5)	40.0 (49.3)
51-65	25.8 (37.4)	19.8 (25.4)	6.6 (8.6)	45.6 (52.1)
>65	24.5 (35.5)	19.4 (26.9)	7.6 (11.5)	43.8 (51.4)
Number of patients starting				
Overall	69.9 (91.2)	59.5 (70.1)	20.7 (26.8)	129.4 (149.0)
RAS-inhibitors	25.3 (48.1)	16.3 (31.0)	9.5 (10.7)	41.7 (49.3)
Statins	25.9 (48.7)	16.1 (33.5)	9.9 (14.0)	42.0 (51.4)
Bisphosphonates	4.8 (8.1)	6.1 (11.4)	5.7 (8.2)	11.0 (11.6)
Antidepressants	13.9 (23.3)	20.9 (40.5)	16.3 (23.4)	34.8 (39.9)
Chronic Disease Score				
0-1	27.3 (33.0)	24.8 (29.1)	7.9 (11.5)	52.0 (59.9)
2-4	27.3 (33.0)	16.9 (22.7)	5.8 (8.3)	38.4 (43.8)
5-19	21.2 (29.5)	16.5 (21.2)	6.4 (8.0)	37.7 (45.0)
Status score				
< -1.0	24.4 (55.4)	20.5 (45.1)	7.7 (18.2)	44.9 (96.1)
-1 to 0.5	24.4 (44.3)	18.0 (29.5)	6.2 (12.2)	42.4 (67.6)
>0.5	21.1 (33.6)	21.1 (35.0)	6.7 (10.7)	42.2 (64.2)

Values are means per cluster (standard deviation) unless stated otherwise.

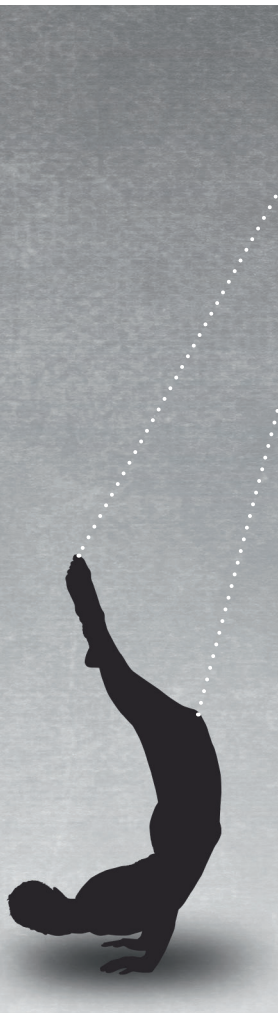
Table 5: Baseline socio-demographic and health characteristics for each group at individual level.

Characteristic	Usual Care	Eligible patients (ITT)	Patients with counselling (PP)	Eligible patients without counselling	Overall
Overall	n=3637	n=3094	n=1054	n=2040	n=6731
Mean (SD) age, years	59.0 (15.1)	56.9 (15.9)	58.6 (15.8)	58.0 (15.5)	56.1(15.9)
Female, n (%)	1987 (54.6)	1785 (57.7)	644 (61.1)	3772 (56.0)	1141 (55.9)
Mean (SD) status score	-0.44 (1.29)	-0.31 (1.20)	-0.43 (1.27)	-0.38 (1.25)	-0.24(1.16)
Mean (SD) CDS	3.3 (3.1)	3.1 (3.1)	3.4 (3.2)	3.2 (3.1)	3.0(3.1)
Starting with RAS-inhibitor	n=1317	n=850	n=257	n=593	n=2167
Mean (SD) age, years	61.1 (13.7)	62.2 (13.0)	63.8 (12.2)	61.6 (13.4)	61.5 (13.3)
Female, n (%)	710 (53.9)	439 (51.6)	145 (56.4)	1149 (53.0)	294 (49.6)
Mean (SD) status score	-0.62 (1.32)	-0.01 (1.06)	-0.08 (1.18)	-0.38 (1.26)	0.02 (1.0)
Mean (SD) CDS	3.3 (3.1)	3.3 (3.0)	3.5 (2.9)	3.3 (3.1)	3.2 (3.0)
Starting with statin	n=1345	n=839	n=268	n=571	n=2184
Mean (SD) age, years	60.6 (12.6)	61.6 (11.5)	62.5 (11.3)	61.0 (12.2)	61.2 (11.5)
Female, n (%)	660 (49.1)	414 (49.3)	139 (51.9)	1074 (49.2)	275 (48.2)
Mean (SD) status score	-0.60 (1.29)	-0.02 (0.97)	-0.01 (0.98)	-0.38 (1.21)	-0.03 (0.97)
Mean (SD) CDS	3.4 (2.9)	3.4 (2.8)	3.6 (2.8)	3.4 (2.9)	3.3 (2.8)
Starting with bisphosphonate	n=252	n=319	n=137	n=182	n=571
Mean (SD) age, years	66.5 (13.4)	66.2 (13.5)	67.8 (12.1)	66.3 (13.5)	64.9 (14.4)
Female, n (%)	186 (73.8)	251 (78.7)	111 (81.0)	437 (76.5)	140 (76.9)
Mean (SD) status score	0.14 (1.12)	-0.54 (1.25)	-0.64 (1.23)	-0.24 (1.24)	-0.46 (1.26)
Mean (SD) CDS	4.8 (3.9)	5.1 (3.7)	5.4 (3.7)	5.0 (3.8)	4.9 (3.7)
Starting with antidepressant	n=723	n=1086	n=392	n=694	n=1086
Mean (SD) age, years	49.4 (17.9)	46.5 (16.1)	49.3 (17.0)	47.7 (16.9)	44.9 (15.4)
Female, n (%)	431 (59.6)	681 (62.7)	249 (63.5)	1112 (61.5)	432 (62.2)
Mean (SD) status score	-0.03 (1.15)	-0.70 (1.33)	-0.89 (1.34)	-0.43 (1.30)	-0.59 (1.31)
Mean (SD) CDS	2.3 (2.9)	2.2 (2.9)	2.4 (3.1)	2.3 (2.9)	2.0 (2.8)

Values at are numbers (percentages) unless stated otherwise.

CHAPTER 5

Does the use of an electronic reminder device with or without counselling improve adherence to lipid-lowering treatment? The results of a randomized controlled trial



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Abstract

Background: The use of lipid lowering treatment with statins has proven to be effective in reducing cardiovascular events and mortality. However in daily practice adherence to medication is often low and compromises the effect of therapy. The aim of this study was to assess the effectiveness of an electronic reminder device (ERD) with or without counselling to improve refill adherence and persistence to statin treatment in non-adherent patients.

Methods: A multicentre, community pharmacy-based randomized controlled trial conducted in 24 pharmacies in The Netherlands, with patients with prior baseline refill adherence rates between 50-80%. Eligible patients of ≥ 65 years were randomly assigned to 1 of 3 groups: (1) counselling with an ERD (n=134), (2) ERD with a written instruction (n=131) and (3) control group (n=134).

Main Outcome Measure: Refill adherence to statin treatment in 360 days after inclusion (PDC360). Patients with a refill rate ≥ 80% were considered adherent. We also assessed the effect among subgroups.

Results: There were no relevant differences at baseline. In the counselling + ERD-arm 54 of 130 eligible patients received the counselling with ERD. In the ERD-arm, 117 of 123 eligible patients received the ERD. The proportions of adherent patients in the counselling + ERD group (69.2%) and in the ERD-only group (72.4%) were not higher compared to the control group (64.8%). Among women using statins for secondary prevention, in the ERD group more patients were adherent (86.1%) than in the usual care group (52.6%) ($p<0.005$). In men using statins for secondary prevention, no effect of the ERD has been found.

Conclusion: In this randomized controlled trial, we found no statistically significant improvement of refill adherence with the use of an ERD with or without counselling. However, in a subgroup of women using statins for secondary prevention, the ERD improved adherence statistically significant.

Introduction

The use of statins has proven to be effective in reducing cardiovascular events and mortality.[1] Despite this beneficial effect, adherence to lipid lowering treatment is substantially worse in daily practice compared to adherence observed in the controlled setting of randomized controlled trials.[2,3] Non-adherence to statins reduces the beneficial effect and increases the risks of cardiovascular events.[4]

Urquhart et al. and more recently Vrijens et al. argued that three phases of chronic drug treatment can be identified: acceptance of the treatment plan, execution of the drug regimen and eventually complete discontinuation (non-persistence) of treatment.[5,6] Non-adherence can take place in these three different stages.[6] In this study we focused on patients being non-adherent in the execution phase and defined it as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen".[7]

There have been numerous attempts to design interventions to improve medication adherence for patients with chronic diseases, with variable rates of success.[3,8-11] Almost all effective interventions were complex, incorporating combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, and other forms of additional supervision or attention by a health care provider.[10,11] Johnson et al examined the application of the full "stages of change model", to increase patients' taking adherence to lipid lowering treatment,[12] and patients who were treated according to this model, were more likely to be adherent at 12, and at 18-months. This model is based on 5 different stages of change: the pre-contemplation stage, contemplation stage, preparation stage, action stage and maintenance stage.[13] In contrast, an intervention as simple as a medication reminder has also been demonstrated to increase adherence to antihypertensive drugs with about 6-8%[14,15] and lipid lowering treatment with 6.5-12%.[16] A medication reminder aims to minimize forgetfulness, a common reason for non-adherence.[17]

Studies based on pharmacy records suggest that these refill data can be used to identify non-adherent patients.[18-20] Community pharmacist could play an important role in improving adherence.[3,21,22] Therefore we used refill data to select non-adherent statins users and designed a pharmacy-based intervention. At least two reasons are identified for adherence improving interventions not to be successful: (1) patients that volunteered to participate in the study were already adherent at baseline[3,23] and (2) participation in the study itself can increase adherence in the control-group (the Hawthorne-effect)[24], thereby decreasing power to detect a significant effect of the intervention. In this study we used a framework that minimizes these two limitations. Firstly, only non-adherent patients were included. Secondly, adherence was assessed objectively with refill data. Finally patients were not aware of study participation, thereby minimizing the Hawthorne effect. The object

of this study was to assess the effectiveness of an electronic reminder device (ERD) with or without counselling to improve refill adherence and persistence to statin treatment in non-adherent patients.

Methods

Study-design

A multicentre, community pharmacy-based, randomized controlled trial (Figure 1).

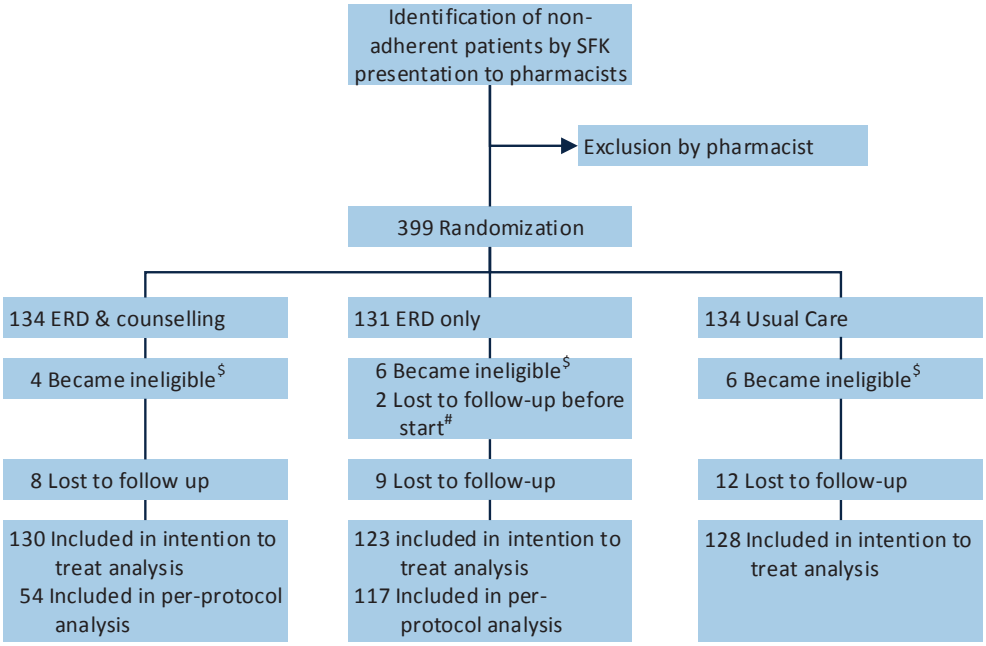

Figure 1: Trial profile.

$ Patients receiving their medication weekly in a dosing cassette or blisterpacks were excluded.

Patients had no refill at all between selection by SFK and start of intervention.

Participants

Patients were selected in 24 community pharmacies in different areas of The Netherlands. We included patients that started statins at least one year prior to inclusion and were non-adherent the year prior to inclusion (refill rate between 50 to 80%). Excluded were patients not personally responsible for their medication intake or received their medication in a dosing aid, patients with a life-expectancy of less than 6 months and patients younger than 65 years. Life-expectancy is difficult to assess but assessment was based on personal

knowledge about the patient and prescription of drugs used in the palliative phase. Also excluded were patients who switched to a different statin in the 540 days before inclusion. General practitioners received general information on the study but were not involved in recruitment nor selection. Patients were not asked to consent to study participation. Patients were recruited between January 2008 and March 2008. The Medical Ethics Review Committee (METC) of the University Medical Centre Utrecht considered our research proposal in the meeting of August 21, 2007 and concluded that the Dutch Medical Research Involving Human Subjects Act (WMO) was not applicable (approval number 07-226) which implied that the committee decided that no approval of the METC was needed. No extra data had to be collected and there was no extra burden for the patients in the usual care group. Patients in the intervention groups had the option to refuse the intervention. The trial was registered at www.clinicaltrials.gov under the identifier NCT00493337. Pharmacists were informed about the study and received instructions about the randomization and the intervention.

Definition of non-adherence for selecting patients

Patients were selected based on refill data and were presented to the pharmacist when they met the following criteria: (1) received a prescription for a statin in the preceding month, (2) received a prescription for the same statin between 12 and 18 months prior to that prescription and (3) had a refill adherence between 50 to 80% of the 365 days prior to the last statin prescription covered by the same statin (see below). For patients with more than 60 *consecutive* days without coverage, (4) an additional refill of a non-statin prescription was required to exclude the possibility that the patient had moved to another pharmacy. Refill adherence was assessed by calculating the proportion of days covered of the 365 days before selection by using the dispensing date and the theoretical duration of a prescription. The latter is assessed by dividing the number tablets dispensed by the number of tablets used daily, both available from the pharmacy computer system. In the Netherlands 95 % of patients collect their prescription drugs in the same community pharmacy.[25]

Patients were identified by an automated search-protocol that was developed by the “Stichting Farmaceutische Kengetallen” (SFK). The SFK collects dispensing data of more than 90% of Dutch community pharmacies. The results of the selection were presented to the pharmacist at a secured website. The pharmacists were asked to assess for each patient if they were eligible. After selection by the pharmacist, patients were randomized in to 1 of the 3 intervention groups.

The 80% cut-off value is the most frequently used value for non-adherence although its clinical relevance depends on the particular medication under study.[26] Karve et al. found

that among patients treated for hyperlipidaemia, a cut off value of 81% was clinically relevant with regard to diseased-related hospitalization.[27] Patients with an adherence of less than 50% were excluded to increase the likelihood that patients were suboptimal users rather than complete discontinuers who restarted treatment.

Randomization

Patients were randomized into one of three groups: the Counselling with Electronic Reminder Device (ERD)-group, the ERD-group (with written instruction) or the Control group (usual care) in a 1:1:1 ratio using a computer generated random number sequence. Patients were randomized in blocks based on baseline medication adherence (above or below 65%) and age (above or below 75 using the minimization method with equal weights assigned to both categories).[28,29]

Intervention

Counselling with ERD-group (1): Patients were invited by the pharmacist by postal mail and a follow-up phone call 14 days after the written invitation. The intervention consisted of two elements: the first and most important element is the application of the stages of change model in non-adherence counselling. The second element is the ERD.

The 10 minute counselling by the pharmacist consisted of five phases. The patient received feedback on their previous drug dispensing data (1). Patients were asked if they were aware that they were non-adherent and reasons for non-adherence were discussed (2). Patients were informed about the benefits of statin-use (3), received an ERD to help them with medication taking (4) and were informed that after one year, the patient would be invited for a follow-up visit(5). The ERD (Compliance Card ®, Figure 2) is a medication reminder device that starts beeping every day at the same time, until the patient switches it off. Patients can adjust the time.

ERD-group (2): Patients received the ERD by mail with a written instruction about the use of the device.

Control Group (3): Patients in the control group received usual care. In The Netherlands usual care can be described as follows: at the start of therapy, patients receive written and spoken information about the therapy and medication. After about 2 weeks, the patient should return for the first refill. At that moment, patients are asked about their experience, concerns and need for information. Patients who use a statin for more than a year, do not receive counselling on a regular basis.

Figure 2: ERD, Compliance Card®.
This credit-card size ERD needs to be activated after the first dose and gives a signal after every 24-h interval following its activation. It actively needs to be turned off. An instruction for the first use is printed on the card.

Outcomes

The pre-specified primary outcome was refill adherence to statins based on pharmacy dispensing records. Refill adherence was assessed by calculating the proportion of days covered of the 360 days following the index date by dividing the total days' supply by the number of days of study participation (PDC360).[30] The index date is the date of the first prescription for a statin after selection by SFK. The total days supplied was calculated as the sum of days dispensed within the study period. If a supply exceeded the end of the study participation, this supply was corrected for exceeding the end of the period. The number of days of study participation was defined as the number of days between the index date and the index date + 360 or the last refill date, whichever came first. For assessing the last refill date, all refills for any drug were included. We analysed refill adherence both as a continuous measure and as a dichotomous measure, the latter with a threshold of 80%: patients with a PDC360 < 80% were defined as non-adherent and patients with a PDC360 ≥ 80% were defined as adherent.

The secondary outcome was the occurrence of complete discontinuation, defined as more than 182 consecutive days (50%) of the one-year observation period uncovered.

Power calculation

With a type one error (α) for a two sided test of 0.05 and a probability of correctly rejecting the false null hypothesis of 0.80 (1-β) 69 patients were needed in each arm of the 3 arms for demonstrating an improvement of the proportion of adherent patients from 65% to 80%.[31] Assuming a dropout rate of 25%,[23] at least 269 patients were required. Each community pharmacist was asked to recruit at least 15 non-adherent patients, 5 patients in each group.

Handling and storage of data and documents

All patient data were provided to the SFK by the participating pharmacies according to an already existing procedure to protect the subjects' privacy. The SFK provided the data to the researchers at Utrecht University. All data with regard to the patients' identity were coded anonymous by the participating pharmacies.

Intention to treat versus per protocol: In daily practice, a health care provider can decide not to follow treatment guidelines or a study protocol. In this study, pharmacist may have had good reasons not to invite a patient after randomization. For example when no telephone number was known to the pharmacist, or when the patient experienced a live event like death of a partner. In the counselling/ERD group, it was to be expected that a part of the patients was not willing to come to the pharmacy for counselling. Since this could introduce a bias, we performed both a per protocol analysis and an intention to treat (ITT) analysis. In the former we included only the patients that received the intervention. In the latter we included all randomized patients, even when a pharmacist decided for a specific patient not to follow the study protocol or when a patient was not willing to visit the pharmacy for counselling.

Statistical analysis

The primary analysis was based on the intention to treat principle. Patient characteristics between groups were compared using Student's t-test or χ^2- test. Because the PDC360 was not normally distributed, we analysed the PDC360 between groups using the nonparametric Mann-Whitney U test (SPSS for Windows version 20.0). We used logistic multilevel analysis to study the effect on the dichotomous primary outcome (MLWIN for Windows version 2.22). The included levels were patient, GP and pharmacist. The secondary outcome of complete discontinuation was assessed using Cox-proportional hazards. We considered a p-value of less than 0.05 to be statistical significant. In a second analysis, the following baseline values were considered as possible confounders and effect modifiers: age, gender, refill rate in 12 months prior inclusion, Chronic Disease Score (CDS), use of beta blocking agents (BBA) or calcium channel blockers (CCB) and use of statin for secondary prevention. The CDS uses drugs dispensed as surrogate markers for chronic illness.[32] Secondary prevention was defined as either concomitant use of one or more platelet aggregation inhibitors (PAI's, ATC-code B01AC) and/or oral antidiabetic drugs (OAD, ATC-code A10B). Effect modification was defined as a significant interaction ($p< 0.10$) between group allocation and the variable in question.

Results

Patient enrolment and baseline

After considered eligible by the pharmacists, 399 patients were randomly assigned to one of the two intervention groups or the Control Group (Figure 1). Two patients were excluded because they did not fill any prescription after the selection date. A total of 16 patients were excluded because they started with receiving medication weekly after the index date.

Patient characteristics and use of medication at baseline are presented in Table 1. Due to missing refill data before inclusion, it was impossible to compare the use of medication of 8 patients in the Counselling/ERD-Group and 2 in the Control Group. Patient characteristics were similar but differences were found for the use of medication. In the ERD-group more patients used BBA's compared to the Control Group and fewer patients in the Counselling/ERD-group used CCB's. The CDS was comparable within the three groups. There were no statistically significant differences in refill adherence before the index date (Mann-Whitney U test). Baseline characteristics were also compared based on per protocol (PP) analysis, but did not materially change our findings (data not shown).

Table 1: Baseline Characteristics of Study Population.

Characteristic	Counselling with ERD (n=130)	ERD only (n=123)	Control Group (n=128)	Overall (n=381)
Mean (SD) age, years	73.3 [6.6]	73.2 [5.8]	73.9 [6.5]	76.5 [6.3]
Male, n (%)	61 (46.9)	53 (43.1)	54 (42.2)	168 (44.1)
Co-medication, n (%)	(n=122)*	(n=123) *	(n=126) *	(n=371) *
Oral antidiabetics (OAD)	26 (21.3)	26 (21.1)	32 (25.4)	84 (22.6)
Insulin without OAD	4 (4.2)	5 (5.2)	5 (5.3)	14 (4.9)
Thiazide diuretics	31 (25.4)	36 (29.3)	31 (24.6)	98 (26.4)
β blocking agents (BBA)	34 (35.2)	62 (50.4)	44 (34.9)	149 (40.2)
Calcium channel blockers (CCB)	11 (9.0)	25 (20.3)	27 (21.4)	63 (17.0)
Nitrates (sublingual)	10 (8.2)	19 (15.4)	12 (9.5)	41 (11.1)
Nitrates (oral, transdermal)	6 (4.9)	11 (8.9)	9 (7.1)	26 (7.0)
Antithrombotics	65 (53.3)	65 (52.8)	65 (51.6)	195 (52.6)
ACE-inhibitors	31 (25.4)	32 (26.0)	41 (32.5)	104 (28.0)
Angiotensin II Receptor Blockers	22 (18.0)	28 (22.8)	25 (19.8)	75 (20.2)
Platelet aggregation inhibitor (PAI´s)	56 (45.9)	55 (44.7)	56 (44.4)	167 (45.0)
Statin, n (%)				
Simvastatin	68 (55.7)	72 (58.5)	78 (61.9)	218 (58.8)
Pravastatin	9 (7.4)	10 (8.1)	7 (5.6)	26 (7.0)
Atorvastatin	26 (21.3)	28 (22.8)	29 (23.0)	83 (22.4)
Rosuvastatin	12 (9.8)	9 (7.3)	10 (7.9)	31 (8.4)
Fluvastatin	6 (4.9)	4 (3.3)	-	10 (2.7)
Simvastatin/ezetimb	1 (0.8)	-	2 (1.6)	3 (0.8)
Chronic Disease Score, mean [SD]	5.0 [2.4]	5.6 [3.1]	5.4 [2.8]	5.4 [2.8]
Refill rate in year prior to inclusion				
50-66%, n (%)	43 (35.2)	48 (39.0)	45 (35.7)	136 (36.7)
67-76%, n (%)	38 (31.1)	34 (27.6)	42 (33.3)	114 (30.7)
77-80%, n (%)	41 (33.6)	41 (33.3)	39 (31.0)	121 (32.6)

*: Missing refill data prior inclusion of eight patients in Counselling/ERD-group, 0 in the ERD-group and 2 in Control Group.

Execution of the interventions

Out of 134 eligible patients randomized to the Counselling/ERD-group, 4 patients became ineligible because they received their medication in weekboxes, 116 patients were invited for counselling, and 14 patients were not invited for counselling (see Figure 3). Of the 14 patients not invited: 2 pharmacists did not register an invitation for any patient for counselling (n=6), 1 pharmacist did register an invitation for 6 patients, and 1 pharmacist excluded 2 patients after randomization. Six pharmacists did not call any patient after the invitation by letter (n=32). 16 pharmacists invited 51 out of 116 patients also by telephone of which 32 (63%) actually received the counselling. Of the 65 patients who were not invited by telephone, 22 (34%) patients received the counselling with ERD. In total 54 of the 116 invited patients (47%) eventually received counselling and the ERD.

Out of the 123 eligible patients in the ERD-group 117 (95%) actually received the ERD. Two pharmacists did not sent any patient the ERD (n=6), but these pharmacists did invite patients for the counselling with ERD intervention.

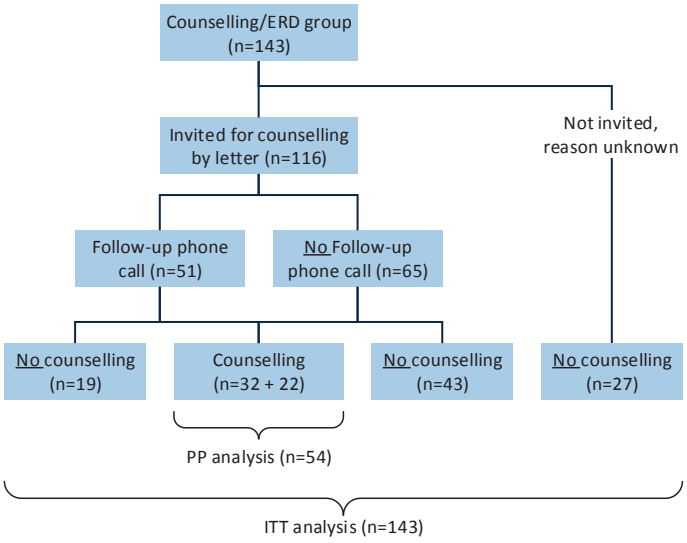

Figure 3: Information about inclusion of patients in ERD/counseling group.

Primary outcome: refill adherence

The median PDC360 was 90.0% (Interquartile range (IQR), 76.8, 98.3) in the Counselling/ERD-group, 91.0% (IQR 76.0, 99.0) in the ERD-group and 87.5% (IQR 75.0, 99.0) in the control group (ITT analysis). No statistically significant differences in the median refill

adherence were assessed (Mann-Whitney U test). Using a cut-off of 80% (PDC360) 69.2% of the patients in the Counselling/ERD-Group were adherent, compared to 72.4% in ERD-group and 64.8% in the control group (Table 2) and these differences were not statistically significant. Since the proportions are high, the presented odds ratios overestimate the relative risk and should therefore not be interpreted as such.[33] A PP analysis yielded that 70.4% of the 54 patients in the Counselling/ERD-Group were adherent and 72.6% of the 117 patients in the ERD-group (Table 2). In a second analysis we assessed the effect of the intervention in different subgroups shown in Table 2. The use of OAD and/or PAIs was a significant effect modifier (p<0.1). In patients not using OAD and/or PAIs there was no statistically significant difference between the ERD-group and the control group. Only in the group of patients using OAD and/or PAIs, gender was a significant effect modifier (p<0.1). In the ERD-group more women using OAD and/or PAI's were adherent (86.1%) compared to the control group (52.6%). This difference is statistically significant (p<0.005). In men using OAD and/or PAIs no effect of the ERD has been found.

Table 2: Results of Multilevel Analyses of the effectiveness of the interventions on proportion of adherent patients (PDC360 ≥ 80%).

Study population *Intervention group*	**No. of subjects**	**No. of adherent subjects (%)**	**Crude model**		**Adjusted model***	
			OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Overall, Intention To Treat						
Control Group	128	83 (64.8)	Ref.	NA	Ref.	NA
Counselling with ERD	130	90 (69.2)	1.22 (0.72,2.06)	0.45	1.18 (0.69,2.01)	0.55
ERD only	123	89 (72.4)	1.33 (0.76,2.32)	0.55	1.49 (0.83,2.69)	0.18
Overall, Per Protocol						
Control Group	128	83 (64.8)	Ref.	NA	Ref.	NA
Counselling with ERD	54	38 (70.4)	1.29 (0.65,2.56)	0.47	1.25 (0.62,2.52)	0.54
ERD only	117	85 (72.6)	1.35 (0.77,2.36)	0.30	1.49 (0.83,2.68)	0.18
Subgroup analysis (based on Intention to treat analysis)						
Primary prevention						
Control group	52	37 (71.2)	Ref.	NA	Ref.	NA
ERD only	51	32 (62.7)	0.68 (0.29,1.57)	0.36	0.60 (0.24,1.48)	0.26
Secondary prevention, women						
Control group	38	20 (52.6)	Ref.	NA	Ref.	NA
ERD only	36	31 (86.1)	**5.58 (1.79,17.4)**	0.003	**8.26 (2.20,31.0)**	0.002
Secondary prevention, men						
Control group	38	26 (68.4)	Ref.	NA	Ref.	NA
ERD only	36	26 (72.2)	1.29 (0.46,3.67)	0.63	1.22 (0.36,4.11)	0.75

Note: OR=odds ratio; CI=confidence interval, ERD=Electronic Reminder Device. Presented odds ratios are the ratios of proportion adherent patients in intervention group versus proportion in Control group. When OR>1: the odds of being adherent in the intervention group is larger than the odds in the control group.

* Adjusted model is corrected for refill adherence in 12 months before index date and use of beta blocking agents (BBA) or calcium channel blocker (CCB).

Secondary outcome: discontinuation

In the Counselling/ERD-Group 6.2% (8) of the patients discontinued treatment with statins, compared to 5.7% (11) in the ERD-group and 9.4% (12) in the Control Group. The adjusted hazard ratio for the Counselling/ERD group versus Control group was 0.67 (95% CI 0.27, 1.6) and for the ERD-group 0.65 (95% CI 0.25, 1.7) (Table 3).

Table 3: The effectiveness of the interventions on proportion of patients that discontinued therapy over time assessed using Cox proportional Hazards.

Group	No. of subjects	No. of discontinued subjects (%)	Crude model		Adjusted model*	
			HR (95% CI)	P value	HR (95% CI)	P value
Control group	128	12 (9.4)	Ref.	NA	Ref.	NA
Counselling with ERD	130	8 (6.2)	0.64 (0.26,1.6)	0.64	0.67 (0.27,1.6)	0.37
ERD only	123	7 (5.7)	0.60 (0.24,1.5)	0.29	0.65 (0.25,1.7)	0.37

Note: *Adjusted model is corrected for age at inclusion

In a sensitivity analysis, we assessed the influence of our pre-specified threshold for optimal refill adherence, and found no influence on our primary conclusion (Table 4).

Table 4: Result of sensitivity analysis: number and percentage of adherent patients when different thresholds were used for the definition of 'adherent'. Analysis based on intention to treat analysis.

Threshold	ERD with counselling (n=130)		ERD only (n=123)		Control Group (n=128)
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)
PDC ≥75%	101 (77.7)	0.96 (0.52,1.77)	98 (79.7)	1.02 (0.92,1.13)	100 (78.1)
PDC ≥80%	90 (69.2)	1.18 (0.69,2.01)	89 (72.4)	1.49 (0.83,2.69)	83 (64.8)
PDC ≥85%	76 (58.5)	1.16 (0.68,1.98)	76 (61.8)	1.48 (0.84,2.59)	70 (54.7)
PDC ≥90%	66 (50.8)	1.26 (0.75,2.13)	66 (53.7)	1.60 (0.94,2.73)	66 (44.5)
PDC ≥95%	49 (37.7)	1.12 (0.67,1.90)	51 (41.5)	1.09 (0.96,1.23)	51 (34.4)

Note: n=number of adherent subjects with the specified threshold. Based on multilevel analysis and corrected for refill adherence in 12 months before index date and use of beta blocking agents (BBA) or calcium channel blocker (CCB).

Discussion

Main findings

In this effectiveness study we compared two interventions, (1) Counselling with an ERD and (2) only an ERD, with usual care and studied the effects on refill adherence and persistence. In the ITT analysis we found a small improvement in refill adherence in the overall population in both intervention groups, but this was not statistically significant. After stratification the effect of the ERD was especially strong in female patients using statins for secondary prevention but not in men. Although this might be a chance finding, we believe there is an explanation for this result. Differences in adherence between groups of patients have been found.[2,34,35] Some recent studies show that women with coronary heart disease[36] or Myocardial Infarction (MI), are less adherent to statins than men. However another study

showed no difference between men and women after MI.[38] Diabetes is an indication to prescribe statins for secondary prevention. Also in this group, women are less adherent than men[39] Gender differences exist in clinical management.[40,41] As far as we know, this gender differences in clinical management have not been studied in the Netherlands, but this might explain the lower adherence in women and consequently the larger effect of the intervention in women using statins for secondary prevention.[18-20] In the control group of our study we also found that women using statins for secondary prevention were less adherent (52.6%) then men (68.4%). So this might partly explain the positive effect in women.

The effects of reminder devices on refill adherence have been studied in populations, including patients with hypertension[14] and patients using statins.[16] In the former the use of an electronic reminder device improved adherence with antihypertensive drug measured over 6 months. After 6 months the device had to be returned to compile the electronic monitoring data. There was a large dropout by patients not willing to use the device, patients who did not return the device or did not provide self-reported adherence. This is different from our study where patients did not have to return the device nor have to fill in a questionnaire. In the study by Vrijens, the intervention was more complex and labour intensive than our intervention in the Counselling/ERD group: at each follow-up visit the data of the electronically compiled dosing history were analysed together with the patient plus in this study a Medication Electronic Monitoring System is used. They found an improvement of adherence mainly by improving persistence. In our study we found no effect of the ERD on persistence (Table 3). Another difference between the two mentioned studies and our study is that we used refill data and not electronic monitoring data.

Strengths of the study

Although the interventions showed no statistically significant improvement in adherence in the overall study population, we showed that a very simple intervention of sending an ERD to nonadherent statin users, can statistically significant improve medication refill adherence in women using statins for secondary prevention. Our study confirms the conclusion of Schedlbauer et al. that reminding patients seems the most promising intervention to improve adherence to statins.[10] Many of the successful adherence improving interventions are time consuming and labour intensive[42] and this hampers implementation in daily practice. Simple interventions that are easy to implement in daily practice both for the patient and the health care professional are most promising in improving adherence.[43] But the challenge is to determine for which group of patients, a simple intervention is effective and which group of patients need more tailored care. An example is the studied intervention with the ERD. This was easy to implement in daily practice and did not require

much more than sending an instruction to the pharmacies and providing the pharmacies with the devices, letters for the patients and tools to select patients. So unlike the counselling intervention, the intervention with the ERD was easy to implement in daily practice.

Limitations of the study

Our study has some limitations. Firstly: some pharmacists did not follow the study protocol and did not invite any patient for the counselling or did not send the ERD with instruction. It appears that some pharmacies did not follow the protocol completely, because they did not register an invitation for counselling, excluded after randomization or did not sent the ERD. Also some pharmacist did not invite the patient by telephone. There can be a good reason not to follow the protocol for individual patient, for example when the patient experienced a life event and adherence is not the most important issue at that moment. In the ITT analysis this diluted the effect of the intervention since all presented patients were included in the analysis. Only 54 patients of the 116 invited patients actually received the counselling. One important reason is that in 65 patients, the pharmacist did not invite the patient by telephone. Apparently, an invitation letter alone is not enough to motivate patients to come to the pharmacy. In the PP analysis we only included patients who eventually received the counselling or ERD. We believe however that the effect of a selection bias is small, since pharmacist did not selectively excluded patients after randomization: they invited all or none. More attention should have been given to the implementation of the intervention with counselling. Secondly, the number of included patients is not quite high which may have caused to little power to demonstrate a statically significant effect. Thirdly, some patients can be selected as being non-adherent while in practice they were more than 80% adherent, for example when they were hospitalized. This is likely to be non-differentially distributed among our trials arms, and thus would only have diluted the effect of the intervention. Fourthly, in both intervention groups it is not known if the patients who received the ERD with the instruction, actually used the device and it is unknown what the opinion is of the patient. In future studies this should be investigated in more detail. Finally, we used a multilevel logistic regression analysis which results in an odds ratio as an effect size. But since the proportions of adherent patients are relatively high, the odds ratio will overestimate the effect size when it is interpreted as a relative risk[33]. So although we can make a statement if there is an effect of the intervention, it is difficult to determine the actual size of the effect.

Implications for practice and research

The results of this study suggest that the use of a simple ERD can improve refill adherence in specific subgroups of patients but not in the overall population. This justifies future studies among these patients, aimed to more accurately quantify the effect in different groups of patients. For designing an intervention with the use of an ERD we advise to focus on persistent, but non-adherent patients. A part of the patients in our study was not motivated to visit the pharmacy for counselling. This group needs attention and perhaps other types of counselling are more appropriate like counselling by telephone or home-visits.

Conclusions

In this randomized controlled trial, we found no statistically significant improvement of refill adherence with the use of an ERD with or without counselling. However, in a subgroup of women using statins for secondary prevention, the ERD improved adherence statistically significant.

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Appendixes

Appendix 1: translated invitation letter for counselling

Dear Sir / Madam,

In the Netherlands more than one million people use cholesterol-lowering agents. You as a user of ..... (simvastatin) are one of them. These drugs should be taken routinely every day. Many patients experience difficulties with this routine.

I would like to invite you to visit the pharmacy and talk about the use of ..... (simvastatin). We can discuss questions regarding this medicine such as possible side effects, doubts about the necessity of treatment or uncertainties regarding the proper use. I am professionally interested in your experience with this drug, both in order to clarify your question as to assure proper counselling for other users of this medicine

I would be very happy to see you in the pharmacy. At the bottom of this letter you will find some suggestions for times available. If none of them is suitable for you, please contact to see if another time is available.

Sincerely,

your pharmacist

Original text in Dutch:

Geachte heer/mevrouw,

In Nederland gebruiken jaarlijks momenteel meer dan één miljoen patiënten cholesterolverlagende middelen. U als gebruiker van ..... (simvastatine) bent hier één van. Deze geneesmiddelen moeten iedere dag ingenomen worden. Uit onderzoek blijkt dat veel patiënten hier moeite mee hebben.

Graag zou ik u willen uitnodigen voor een gesprek om langs te komen in de apotheek en te praten over het gebruik van ..... (simvastatine). Wellicht heeft u vragen over dit geneesmiddel, heeft u bijvoorbeeld last van bijwerkingen of twijfelt u aan de werking of het nut. Tijdens dit gesprek kunt u dit allemaal ter sprake brengen. Voor mij als apotheker is het ook belangrijk om te weten hoe dit soort geneesmiddelen in de praktijk gebruikt worden en of er problemen zijn die goed gebruik in de weg staan. Dat wil ik graag van u als gebruiker horen.

Onderaan deze brief vindt u een aantal tijdstippen waarvoor u een afspraak kunt maken door met uw apotheek te bellen. Mogelijk zit er geen tijdstip bij waarop u kunt. Na overleg met u kan er dan een ander tijdstip afgesproken worden.

Met vriendelijke groet,

Uw apotheker

Appendix 2: translated information letter for ERD-only group

Dear Sir / Madam,

In the Netherlands more than one million people use cholesterol-lowering agents. You as a user of ..... (simvastatin) are one of them. These drugs should be taken routinely every day. Many patients experience difficulties with this routine.

To facilitate your routine, we sent you a device. This device is designed specifically for people who need to take medicines every day. It gives a signal at a chosen moment at which you prefer taking your medicines. The next time you have to take ..... (simvastatin) you can activate the device by pressing and holding this button, you will hear a beep. Thereafter, this device will remind you every day at the same time. You can turn off the device by pressing the button. I hope this device helps you to take ..... (Simvastatin) daily. There are no costs charged for this device.

If you have any questions regarding this letter, please do not hesitate to call or come by.

Sincerely,

your pharmacist

Original text in Dutch:

Geachte heer/mevrouw,

In Nederland gebruiken jaarlijks momenteel meer dan één miljoen patiënten cholesterolverlagende middelen. U als gebruiker van ..... (simvastatine) bent hier één van. Deze geneesmiddelen moeten iedere dag ingenomen worden. Uit onderzoek blijkt dat veel patiënten hier moeite mee hebben.

Om u te helpen met de dagelijkse inname ontvangt u een apparaatje. Dit apparaatje is speciaal ontwikkeld voor mensen die dagelijks medicijnen moeten innemen. Dit apparaatje geeft op een door u ingesteld tijdstip een signaal af. De eerstvolgende keer dat u ……(simvastatine) inneemt activeert u het apparaatje door de knop ingedrukt te houden, u hoort dan een piepsignaal. Vervolgens zal dit apparaatje u elke dag op hetzelfde tijdstip waarschuwen. Op deze manier wordt u er iedere dag aan herinnerd wanneer het tijd is ..... (simvastatine) weer in te nemen. U kunt het apparaatje dan uitzetten door nogmaals op de knop te drukken. Ik hoop dat dit apparaatje u helpt om ..... (simvastatine) dagelijks in te nemen. Er zijn voor u overigens geen kosten verbonden aan dit apparaatje.

Als u nog vragen heeft naar aanleiding van deze brief, dan kunt u natuurlijk altijd even bellen of langskomen.

Met vriendelijke groet,

Uw apotheker

CHAPTER 6

General discussion

General discussion

Numerous randomized controlled trials have demonstrated the efficacy of medication in reduction of morbidity, mortality and improvement of quality of life in diverse therapeutic areas. Under highly controlled circumstances and after selection of specific patients, adherence to prescribed therapy may be high, but unfortunately in clinical practice much lower adherence rates have been systematically reported.[1-5] Adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behaviour - taking medication - corresponds with agreed recommendations from a health care provider".[6] Medication adherence is primarily important for individual patients since treatment goals will frequently not be achieved when medication is taken insufficiently or incorrectly. Also from a societal perspective medication adherence is important. Non-adherence to medication is associated with reduction of clinical outcomes, hospital admissions, higher health care and societal costs.[2,7-14]

Improving medication adherence is difficult, as is any type of health behaviour. Medication adherence is influenced by numerous factors,[15] of which some can be altered while others cannot, or only with considerable effort. Obviously, the ultimate moment of drug-intake lies with the patient, but adherence cannot exclusively been considered a patient's responsibility. Two other relevant domains are the health care providers including physicians, nurses and pharmacists who contribute to optimal adherence and the health care system that should support both patients and providers to implement interventions to improve adherence.[16]

Although some professional guidelines have started to pay attention to the relevance of medication adherence,[17] systematic assessment and improvement of adherence remains far from being usual care. During interactions between patients and physicians the subject is often avoided.[18-20] Both physicians and pharmacists may address adherence at different stages of the patient's treatment. The start of therapy is a crucial moment to involve patients in the decision making process and to support patients to become adherent to the agreed treatment. But care does not stop at the start of a treatment: adherence should be continuously monitored and patient's beliefs about and experiences with medication should be assessed periodically.

This thesis focuses on the pharmacist's role in supporting patients' medication adherence, at the start, but also during the implementation phase of drug therapy.

Our first study demonstrated that pharmacists currently predominantly have a reactive role. Most private face-to-face and telephone consultations between pharmacists and patients, were initiated by the patients (**Chapter 2**). Pharmacists mostly initiated consultations based on computerised alerts (e.g. regarding drug-drug or drug-disease interactions). A pro-active approach by the pharmacist was studied in **Chapter 4** where

pharmacists called patients who recently started their medication therapy. The trial design is presented in **Chapter 4.1**. Patients who received telephone counselling at the start of therapy were more satisfied with counselling in general and were more satisfied with information (**Chapter 4.4**). These effects were more pronounced in men than in women. **Chapter 4.5** demonstrated that telephone counselling resulted in a clear improvement of adherence to RAS-inhibitors and in an intermediate improvement for statins and bisphosphonates. However, no effect of telephone counselling was found for antidepressants. Treatment fidelity of the intervention was sufficient (**Chapter 4.2**). Analysis of recordings of calls demonstrated that most items of the interview protocol were discussed but that perceptual barriers were not always discussed (**Chapter 4.3**). Older patients were more often reached compared to younger (<65) patients (**Chapter 4.2**).

The role of the pharmacist in improving medication adherence in non-adherent patients who used statins either for primary or secondary prevention, was studied in **Chapter 5**. Providing an electronic reminder device improved adherence only in women using a statin for secondary prevention. Dispensing data of pharmacies were used to calculate medication adherence. In a separate study we showed that standardization of definitions is needed when calculating adherence based on drug utilisation data (**Chapter 3**).

This general discussion will elaborate on the results described in this thesis and place these in a broader perspective. Firstly, the execution of trials in pharmacy practice will be discussed including some aspects on trial design. Secondly, some thoughts and implications for using pharmacy dispensing data as measure for adherence are proposed. Thirdly, thoughts about optimizing care and targeting adherence interventions will be discussed and finally implications for future research and clinical practice will be presented.

Pragmatic or explanatory trials in pharmacy practice

In this thesis, the results of two randomized controlled trials (RCTs) are presented. In designing trials, the balance between internal validity (reliability or accuracy of the results) and external validity (generalizability of the results) is delicate. Over the past decennia RCTs have become the gold standard to study the efficacy and effectiveness of interventions including treatment with medication. RCTs can have an explanatory or pragmatic approach.[21] Explanatory trials test efficacy which is the effect of an intervention under ideal, highly controlled conditions with highly selected participants.[22-24] Poorly adherent patients and those with conditions which might dilute the effect, are often excluded.[21] In general, the internal validity of explanatory trials is high, whereas external validity and the generalizability of the results are low since these highly controlled

conditions do not reflect clinical practice. Pragmatic trials on the other hand, test the effectiveness of an intervention under 'real-world' conditions.[22,24-27] Although generalizability is higher compared to explanatory designs, the conditions are less controlled and execution of the intervention is monitored less strictly, which reduces internal validity. Therefore both types of trials are important and answer different research questions.[26] Although some trials might be very explanatory or very pragmatic, trials can also be positioned somewhere on the pragmatic-explanatory continuum.[21,28,29] Furthermore on some aspects a trial can have an explanatory attitude while on other aspects a more pragmatic approach. Therefore Thorpe et al. introduced the pragmatic-explanatory continuum indicator summary (PRECIS) tool.[28] This tool scores a trial design on ten domains with a score per domain ranging from 1 to 5 and a total score ranging from 10 (most explanatory) to 50 (most pragmatic) (see Table 1 in Appendix). These scores can be graphically presented (see Figure 1).[29]
To our knowledge this tool has not (yet) been applied to trials in pharmacy practice. The following paragraph will elaborate on these domains focussing on trials aimed at improving adherence in pharmacy practice and using the TelCIP trial (**Chapter 4**) and the ERD trial (**Chapter 5**) as examples.

The first domain is the **eligibility criteria of patients**. Explanatory trials in its purest form use strict eligibility criteria by selecting patients with the highest risk of the unfavourable outcome, who are likely to respond to the intervention and are adherent to the therapy. Pragmatic trials on the other side of the spectrum select all patients with the condition of interest, regardless of their anticipated risk, responsiveness, co-morbidities, or past adherence. On this domain, the ERD trial (**Chapter 5**) seems more explanatory since only non-adherent patients were selected for the intervention based on the dispensing data pharmacies have available. However, no strict inclusion criteria were used for co-morbidities or likeliness to respond to the intervention. The TelCIP trial (**Chapter 4**) was more pragmatic as all patients starting with medication were selected irrespective of their history.

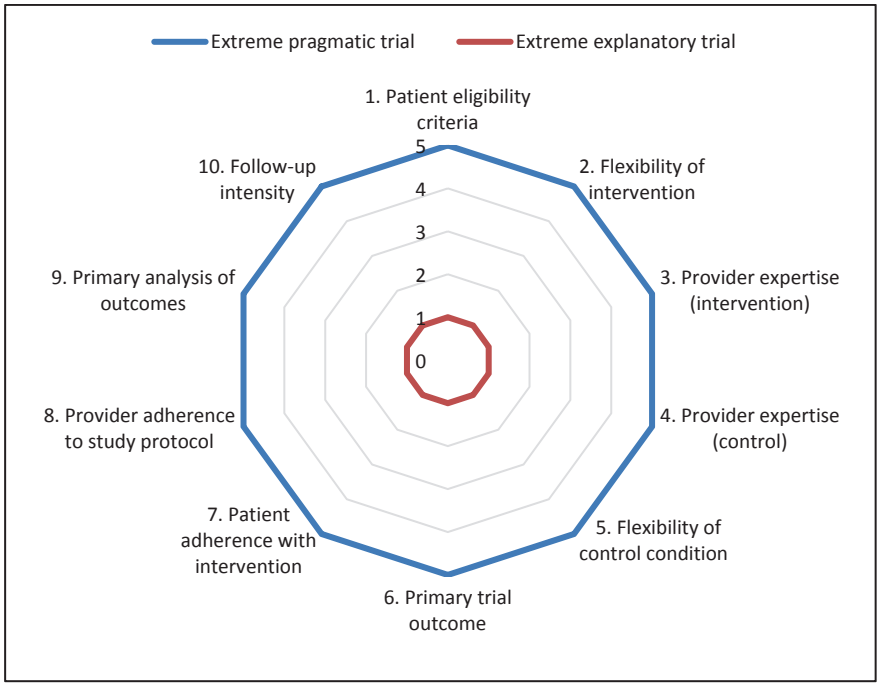

Figure 1: Example of presentation of an explanatory and a pragmatic trial in its purest form[29].

Related to this domain is the **primary analysis of outcomes**. In trials with a pragmatic focus, all patients are included in the analysis regardless of the adherence to the intervention and eligibility (intention-to-treat analysis). In explanatory trials both an intention-to-treat analysis as explanatory or subgroup analysis are performed. The explanatory approach can help both research and clinical practice to target interventions to patients who benefit the most.

In explanatory trials the intervention is strict and **flexibility of the intervention** is low, while the more pragmatic approach allows for more flexibility. This is especially useful in trials aimed at improving medication adherence which is a multidimensional problem. Most of the effective interventions in improving adherence are multifaceted.[30-34] The intervention studied in the TelCIP trial (**Chapter 4**) consisted of counselling in which the pharmacist was stimulated to assess possible barriers for adherence and provide additional support. But it is not always necessary to use a flexible, multifaceted intervention; if the eligibility criteria are strict and patients can be included based on a specific reason for non-adherence, a less flexible intervention can be used. For example if it is obvious that forgetfulness is the most important reason for non-adherence, than an intervention like providing an electronic reminder device (ERD) can be effective. In the ERD trial (**Chapter 5**) both approaches were tested: in one arm a non-flexible intervention

was tested (provision of an ERD to non-adherent patients) while in the other intervention arm a more flexible intervention was tested (provision of an ERD combined with counselling to non-adherent patients). However in the ERD plus counselling arm, part of the patients was not willing to participate and visit the pharmacy for counselling.

This relates to the domain of **patients' adherence to the intervention**. This domain is of interest for interventions focussing on medication adherence. In explanatory trials patients' adherence to the instructions are strictly monitored and can even be a pre-requisite to be allowed to participate in the trial. This may result in selection of patients with lower risk of non-adherence, which, of course, is undesirable in studies that aim to improve adherence.[35,36]

In the ERD trial not only some patients were reluctant to participate, **provider's adherence** to the trial protocol was also low. Pharmacists were expected to invite patients first by post mail and in case of non-response remind patients by telephone. However, only 43% of the non-responders were actually invited by telephone. A more explanatory approach aimed at increasing **provider's adherence** was used in the TelCIP trial: pharmacists' adherence to the trial protocol including the interview protocol was monitored using self-reports. **Provider's adherence** is an important part of treatment fidelity, which has been assessed for the TelCIP trial (**Chapter 4.2**). Treatment fidelity involves the ongoing assessment, monitoring and enhancement of the accuracy and consistency of an intervention to ensure it is implemented as planned and that each component is delivered in a comparable manner to all study participants.[37,38] Treatment fidelity helps to reduce the risk of wrong assumptions of the true intervention effect. Imagine a trial demonstrating significant effects of an intervention. Without information on treatment fidelity, these results can be due to an effective treatment but also to unknown factors that may have been unintentionally added to or omitted from the treatment.[37] And, on the other hand, when no significant results are found, this can be due to a lack of treatment fidelity instead of the treatment being ineffective. Treatment fidelity also places researchers for a dilemma: on one side, it is important to improve internal validity and ensure the intervention is implemented as planned. But on the other hand, the activities used to improve fidelity can also change clinical practice too much and compromise generalizability.

The same dilemma relates to another domain of the PRECIS tool; the **provider experience**. Extensive training and skills assessment, will improve fidelity, but it might compromise the generalizability. In the ERD trial, pharmacists were not trained and only received a written instruction. Starting point for the TelCIP trial was also to study the effect in a 'real-world' situation. Pharmacists received a short communication training but effects of the training were not assessed. Some interactions with patients were recorded

(**Chapter 4.3**) and provided information about the content of the call and the communication skills. However, this information was not used to give feedback including benchmarks to pharmacists in order to stimulate a uniform delivery of the intervention. This might have compromised internal validity, but on the other hand probably improved external validity.

Dispensing data in pharmacies are collected routinely and are therefore very useful as objectively measured **outcomes** of medication adherence. The data can also be used to assess other outcomes like guideline adherence and medication safety (e.g. analysis of the following of treatment guidelines regarding gastro protection in patients with high risk of upper gastrointestinal events).[39-39-41] The use of dispensing data to assess medication adherence will be discussed below in more detail. Although adherence is not a clinical outcome itself, numerous studies demonstrated the relation between medication adherence and clinical relevant outcomes.[2,8-12,42]

The position of both trials on the **follow-up intensity** domain is more obvious: dispensing data were routinely collected and no additional follow-ups were required; the features of a pragmatic trial. In explanatory trials patients are followed with many more frequent visits than would occur in routine practice.

The last two PRECIS domains to be discussed are the **flexibility of the control condition** and **provider expertise on the control condition**. In pragmatic trials, usual care or the best available alternative are generally the control condition, while in explanatory trials a placebo or an active comparator arm are used. Essential in a trial design is a correctly performed randomization process preferably on the patient level. However, randomization at the patient level may not always be the most obvious choice, especially in complex care or behavioural interventions. In these type of interventions randomization on patient level may introduce contamination of control patients. When health care providers are trained to deliver a certain intervention it is conceivable that the acquired skills will also be used in control patients. An alternative is randomization at cluster level (e.g. the pharmacy or the general practice). Advantages of randomization at cluster level are the improvement of feasibility and reduction of risk of contamination. A disadvantage is that a larger number of patients is needed, due to variation among patients within clusters, but also due to variation in outcome between clusters.[43]

In the ERD trial randomization was performed at patient level and in every pharmacy, patients were randomized, after assessment of eligibility, into the usual care arm or one of two intervention arms. Randomization at patient level was chosen since the risk of contamination was low. **Provider expertise** was not relevant in the ERD arm and it was not likely that the expertise for the counselling arm was used for patients in the usual care arm since patients were invited to visit the pharmacy for counselling and the counselling

was not provided to all patients. Due to the nature of the telephone counselling intervention at the start of therapy in the TelCIP trial, the risk of contamination was higher. Moreover pharmacists received additional training and were supported with an interview protocol. To reduce the risk of applying this **provider expertise in the comparison arm**, cluster randomization was used. A disadvantage of the traditional cluster randomization is that when pharmacists are enthusiastic to participate, it can be disappointing to be assigned to the usual care arm. Therefore in the TelCIP trial a cluster randomization was used with two intervention arms and two usual care arms. The choice of intervention arm (medication class) was randomized, but each participating pharmacy included both intervention and control patients (see Figure 2).

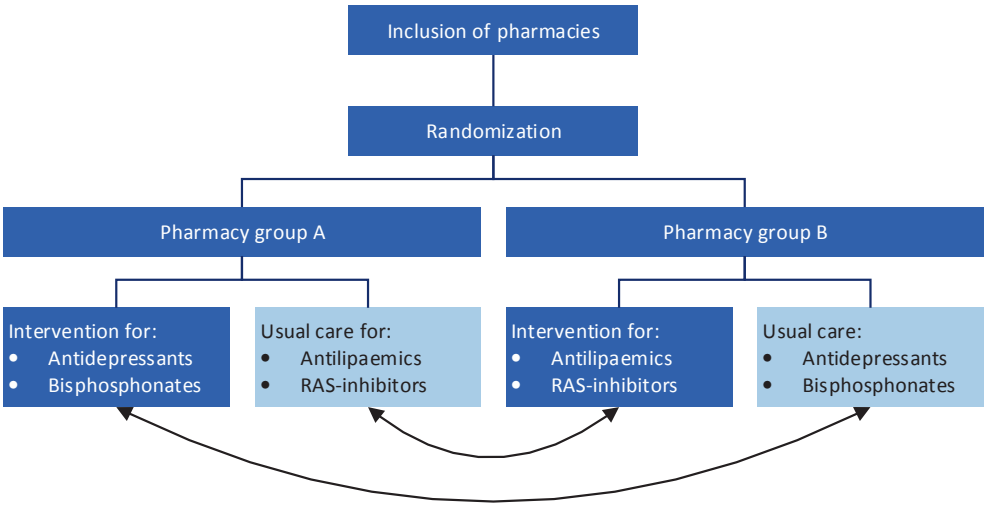

Figure 2: Trial design of the TelCIP trial.
Both groups provided the intervention for two medication classes and usual care for two other medication classes. The choice of medication class is assigned randomly.

This design has an additional advantage as more patients can be included in the same number of practices. The design can also be applied to answer other research questions. In the TELCIP trial patients and pharmacies were randomized at medication class level, but it would also be possible to randomize on patient characteristics. For example by implementing an intervention in one arm for younger patients and in the other arm for older patients. This type of design can be useful to study in which population an intervention works best.

Assessing medication adherence using dispensing data

When treating patients with for example cardiovascular drugs the primary goal of the treatment is not adherence to medication or even lower blood cholesterol or blood pressure, but a reduction of morbidity and mortality. Adherence is merely an essential step on the pathway to reach the primary goal. Assessing the effects of drug therapy on clinical outcomes requires large trials with many follow-up visits and long follow up periods. Since numerous studies demonstrated the association between adherence and clinical relevant outcomes[2,8-12,42] using medication adherence as primary outcome provides a useful alternative.

Assessment of medication adherence is needed to 1) describe adherence on a population level, 2) as an outcome in a trial, 3) as a predictor of clinical outcomes or 4) at patient level to monitor adherence and target interventions. Different methods can be used to assess adherence. For example by direct observation, self-report, pill-counts, Medication Event Monitoring Systems (MEMS), prescribing data, pharmacy dispensing data, claims data or even biochemical measurement as proxies to adherence. All methods have their strengths and weaknesses.[44] Dispensing, prescribing or claims data are frequently used because these are routinely collected and therefore easy accessible, cheap, objective and non-invasive. The major two weaknesses of using dispensing data to assess medication adherence are that they only describe dispensing, not actual intake behaviour and that (a change in) the agreed treatment is not always accurately registered. Irregular refills generally suggest irregular intake behaviour, but can also have a wide array of plausible explanations (e.g. hospitalization or incorrect or incomplete registration of the dosage regimen in the physicians' or pharmacy information system). Difficulties in interpreting these data may also arise when a patient is combining two therapies or switches from one medicine to another. Moreover dispensing data do not enable the measurement of the actual timing of medication intake or if the dosing instructions are followed adequately. So it must be kept in mind that a low refill rate or apparent discontinuation based on dispensing, prescribing or claims data, not necessarily equals non-adherence respectively non-persistence.

Pharmacy dispensing data are mostly used to calculate a so-called possession ratio (the number of days for which medication is supplied divided by the number of days the patient is expected to use the medication).[44-47] However numerous methods for calculating adherence have been identified.[44-46] Frequently used methods are the MPRm (Medication Possession Ratio, modified) and the PDC (Proportion of Days Covered)[48] (see Figure 3). In literature sometimes the same term is used for different calculations. In all methods assumptions have to be made, for example about cut-off points and how to deal

with oversupply. Therefore standardization for some of these assumptions were proposed in **Chapter 3**.

$$MPRm = \frac{Total\ days\ supply - last\ days'\ supply}{(last\ supply\ date - first\ supply\ date)} * 100\%$$

$$PDC = \frac{Total\ days\ supply}{Number\ of\ days\ in\ study\ period} * 100\%$$

Figure 3: Definition of two frequently used formulas to calculate adherence ratios.

Both calculations do not take in to account any change in adherence over time. Consider the following two patients with both four prescriptions but different dispensing patterns (see Figure 4).

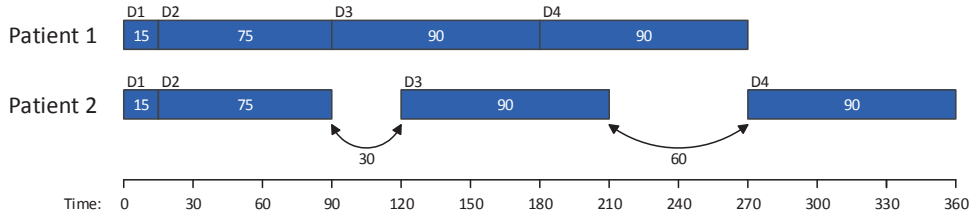

Figure 4: Example of dispensing data of two patients. D1 is first dispensing date, D2, second date etc. The bars represent the number of days supplied.

For both patients the total number of days supplied in the 360 days is the same (270). Using the PDC formula this will result in the same outcome for both patients (270/360=75%), although the dispensing patterns are different. Using the MPRm the number of days supplied of the last supply (no. 4) is distracted from the numerator which result in an MPRm of 100% (180/180) for patient 1 and an MRPm of 67% (180/270) for patient 2.

Even within one formula, the terms can be interpreted differently, take for example the term “last days’ supply”. Looking at patient 2 in Figure 4, prescription number 4 can be interpreted as the last dispensing date but it is also justifiable to regard prescription number 3 as the last dispensing of an episode if a gap of 60 days is considered as (temporary) discontinuation. So the “last day’s supply” can be defined as the supply filled at the last dispensing date within the study period irrespective of a gap followed (no. 4 in Figure 4) but also the last day of a treatment episode[49] or the dispensing date that is followed by exceeding a maximum allowed gap, or ‘treatment gap’. The length of the

episode is influenced by the definition of 'treatment gap'.[49] Van Wijk et al. demonstrated that a smaller maximum allowed gap leads to a lower proportion of patients classified as persistent.[50] The size of the maximum allowed gap will also influence which date is defined as the last supply date and will therefore also influence the calculated ratio, which will generally be lower when longer gaps are allowed.

This example demonstrates what Hess et al. have published before; using different formulas on the same data results in substantial variation in the calculated adherence rates.[45] Numerous papers have been written on the pros and cons of the different formulas to calculate adherence.[44,45,48,51-53] The choice for a certain calculation will depend on the research question, study design, population and resources,[44] however it would be desirable that in research a limited number of definitions is used to describe medication adherence based on pharmacy dispensing data and moreover that researchers clearly explain the method chosen. **Chapter 3** suggests items that have to be reported in studies using dispensing data.

Instead of trying to capture medication-taking behaviour in one number, it might be more useful to combine for example both MPRm and PDC. This best illustrated in a scatterplot where every dot represents a patient (see Figure 5). Both were calculated using a period of 360 days and for MRPm the maximum gap allowed was 90 days. Based on this combination, different groups of patients can be distinguished. For example when both the MPRm and PDC are high (blue circle), this means that patients managed to be adherent the whole year. But when the MPRm was high and the PDC low (green circle), this means that for a period the patient was adherent, but then stopped using it. An MPRm of 0% indicates that the first dispensing was followed by a gap of at least 90 days. Within this group, patients with a low PDC did not reinitiated treatment (brown circle). But when the PDC is high, it means that the patient started using it again after the first gap of 90 days (purple circle). Patients in the yellow circle have an adherence rate somewhere between 60% and 80% for both methods, which is an indication that it is used for a longer period, but with regular gaps all smaller than 90 days.

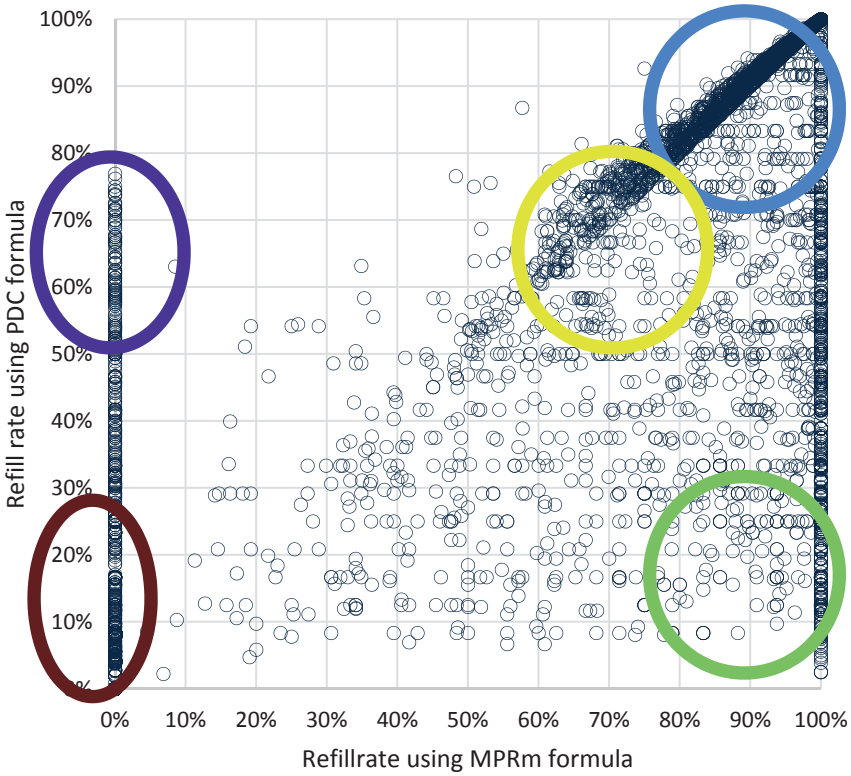

Figure 5: Result of combination of two adherence measures (PDC and MPRm).

Using the two different calculations provides more information, which can help targeting interventions. For example patients in the blue and green circle both have an MRPm between 80% and 100%, but patients in the green circle have low PDC and probably discontinued treatment shortly after the initiation while patients in the blue circle are still using the medication. Patients in the yellow circle and the purple circle both have a PDC between 50% and 80%, but patients in the yellow circle might have problems using the medication regularly while patients in the purple circle probably had some difficulty initiating treatment but now seem to be right on track. A combined approach can help health care providers to focus on specific groups of patients and to tailor interventions to patient needs. Researchers can use this combined approach to differentiate in types of non-adherence and relate this to other potential determinants of non-adherence such as beliefs about medication or outcomes of non-adherence such as disease control or hospitalization.

Optimizing care and personalized medicine

Treating a condition with medication is a process consisting of different steps and activities (see **Figure 6**). Next to the patient several other persons are involved in this process including physicians, pharmacists, nurses and patients relatives. Addressing the 'weakest' link in this chain, might improve adherence, but only as good as the next 'weakest' link. So when trying to promote adherence one should pay attention to all steps and all participants in this process.

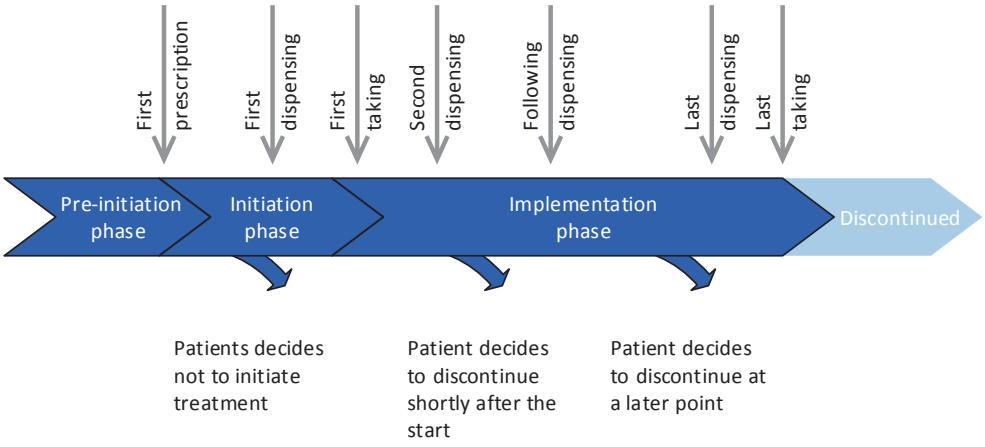

Figure 6: Process of implementation of medication therapy.
The initiation phase starts with the first prescription and ends when the patient takes the first dose. The implementation phase ends with the last dose taking.

The initiation phase in general starts with a physician's diagnosis leading to a prescription. The patient presents the prescription to the pharmacy in order to be filled. The pharmacist should provide the prescribed medicine with sufficient information and instructions for use, enabling the patient to make an informed decision when starting therapy. After the first medication intake the implementation phase starts. Intermittently the patient will have interactions with the diverse health care providers (physician, pharmacist or other health care providers). Regular monitoring during the implementation phase is recommended.

Initiation phase

Four characteristics for SDM:
1. At least two parties are involved
2. Both parties play an active role in the process
3. Information is exchanged both ways
4. Both parties agree on the treatment decision

One of the first decisions a patient has to make is to initiate (or reject) treatment. The decision making process is described in three phases: information exchange, deliberation of treatment options and deciding on treatment to implement.[54] Both providers and patients can take different roles in this process. Charles et al. describe three models used for decision making.[54,55] In the traditional, paternalistic model, the information exchange is one way, from health care provider to patient. The information of the patient is more or less disregarded. The patient is passive and has a dependent role and the physician makes the diagnosis and decides what is best for the patient. The patient has no role in the deliberation process and the decision on the treatment. The informed model is on the other side of the spectrum. Exchange of information is also one-way and largely from physician to patient. In this model the provider provides the information about different treatments and the patient does not share its preference. Technically the patient can make a decision without the provider. This model is premised on the assumption that information is an enabling strategy, "empowering" the patient to become a more autonomous decision maker.[55] "Empirical research demonstrates that many patients, for whatever reasons, prefer not to assume full decision-making control. But many may also not like the idea of having no say at all."[55] Therefore the shared decision-making (SDM) model is in between both sides of the spectrum. This model recognizes the inequality of information and the information exchange is two ways. Both patient and physician play a role in the deliberation and the decision. The way the patient is involved in the decision-making process influences medication adherence.

The obvious next step in the process is filling the prescription in the pharmacy. Some patients however do not to fill their prescription.[56,57] A recent study in Denmark indicated that on average 9.3% of the first prescriptions are not filled.[57] A limitation of this Danish study is a lack of information about the agreement with physician and patient about the treatment.

For the patients who present their first prescription to the pharmacist, pharmacists are well positioned to provide information[58-60] and instructions but also to assess both practical and perceptual barriers that may hamper implementation of the agreed treatment plan.[58] Ideally, the pharmacist supports the patient in this implementation. However, since the pharmacist holds (partially) different information and knowledge compared to the physician[61] it is possible that the information provided influences the

deliberation process and the decision. For example if the prescribed regimen is unlikely to fit in to the life of the patient, the patient can decide not to initiate treatment. Communication between physician and pharmacist is crucial in this respect. Due to design of the current medication prescribing process, extension of shared decision-making to pharmacy practice is a major challenge. In the ideal situation pharmacists participate in SDM in good harmony with prescribers, integrating their specific knowledge, competences and experience in the process.

Research demonstrates that usual care at the start of therapy is not as it should be: SDM is not yet routinely implemented in daily clinical practice,[62] education at that start of therapy is not optimal[63-65] and services are not tailored to patient's needs.[66,67] Pharmacists can pursue a more active role at the initiation of drug therapy for example by providing structured care as currently studied as part of the UK's New Medicines Service (NMS).[68] A similar pro-active role in supporting patients at the start of therapy was studied in the TelCIP trial which demonstrated an improvement of satisfaction with information, reduction of concerns (**Chapter 4.4**) and improvement of adherence (**Chapter 4.5**).

It is a challenge to target this comprehensive care to patients who are most likely to benefit. For some patients visiting the pharmacy with a first prescription, standard care is sufficient and counselling by telephone might be redundant. Others might need additional care. For example when a patient has low literacy skills, high concerns or does not have the opportunity to visit the pharmacy. Lack of competencies, time and knowledge of the health care provider may also render usual care insufficient. In such cases additional service like telephone counselling can be effective.

Variability in standard care between patients but also between health care providers influences the effectiveness of an intervention.[69] Unfortunately in the TelCIP trial, the quality of usual care was not measured. Therefore, we could not assess whether the intervention was more effective in patients who received inadequate usual care compared to patients who received sufficient usual care. In other words, we do not know if the intervention was effective for all patients, or only for those patients who, for example, were unable to visit the pharmacy. Nonetheless, the TelCIP trial demonstrated that more men thought this service had an added value compared to women. Moreover it improved satisfaction with information in men whereas there was little effect in women. Men in the usual care group were less satisfied than women receiving usual care (**Chapter 4.1**). One practical explanation can be that men visit the pharmacy less frequently and more frequently have someone else picking up their medication. And thus more often state not to have received information. Sparse data support this theory, but in Northern Island women visit the pharmacy more frequently than men[70] and a study focusing on the New Medicines Service (NMS) indicated that 28% of the prescriptions were collected by patient

representatives or proxies.[71] A recent Dutch study demonstrated that about a third of visitors of the pharmacy, were collecting medication for someone else.[64] Difference in effect can also be explained by difference in communication style[72-74] and preferences.[75,76] Most research in pharmacy focussed on one-way communication[77] and we found no information on the communication-dyad in pharmacies, however it is plausible that gender difference also play a role in the pharmacy, especially since most Dutch technicians are female and most counselling is done by those technicians.

Implementation phase

The next step in the process is the implementation of the therapy once it is started. In this phase it is important to monitor taking behaviour and disclose emerging barriers like low necessity beliefs, concerns or experience of side effects in order support the patient to adhere to the treatment. Research demonstrated that adherence is not a standard topic in interactions between patients and physicians.[18,19] Health care providers should inquire about patient experiences and beliefs about therapy periodically as well as inquire how patients are coping with the medication, how and when they take it. Additionally, pharmacists can use dispensing data to address adherence, at the first refill but also at subsequent fills. Some pharmacy information systems indicate when patients return for a refill later than expected which should be a trigger to start a discussion with a patient about medication-taking behaviour. However little is known on how pharmacists exploit this feature of their information systems. Moreover some patients do not return for a refill at all. Therefore it should be periodically checked if a patient is still on treatment. Stuurman et al. studied an intervention using dispensing data to screen periodically for patients who are likely to have discontinued treatment. This approach has been proven to be (cost) effective in improvement of adherence (persistence) with bisphosphonates[78] and statins.[79]

Targeting interventions is also important in the implementation phase. One example of targeting emerges from the ERD study (Chapter 5). In most studies women seem to be more adherent compared to men. However, other studies demonstrate that women using statins for secondary prevention were less adherent than men.[80-82] In the ERD study, women in the control group were less adherent compared to men, which resulted in a significant improvement in adherence by providing the electronic reminder device (ERD). But it is not likely that women using statins for secondary prevention are more forgetful than men. Other explanations may be more likely. The difference in effect of the intervention can be influenced by the perception and beliefs of both patients and health care providers. Coronary heart disease (CHD) is mostly seen as a ‘male’ disease. This results in difference in the treatment of men and women.[83] This difference in treatment

may affect patients' perception, beliefs about medication and motivation at baseline. Perhaps our intervention improved adherence by improvement of necessity beliefs: "The pharmacist really thinks this is important, so maybe it really is…" So instead of providing a reminder device to all non-adherent women using statins for secondary prevention, it might be better to improve standard care.

Supporting providers to provide optimal care

Health care providers can support patients to adhere to the agreed treatment. But also for the health care provider, barriers exist that hamper implementation of optimal care. Supporting medication-taking behaviour requires a competent health care provider who is able to alleviate potential barriers for optimal adherence. In the TelCIP trial a patient-centred interview protocol was used to facilitate providers during counselling. Voice recordings in a sample of pharmacies showed that mainly practical barriers were discussed. Most pharmacists had trouble with discussing perceptual barriers (**Chapter 4.3**). In addition, in the registration data (**Chapter 4.2**) we found that knowledge items were more frequently discussed than perceptual barriers and experiences, which is in line with a recent trial using video-recorded first prescription encounters.[64]

Also the provider has beliefs about the treatment and absence of a perceived need to use a certain treatment and (sometimes irrational) concerns about the (long term) threats of using medication can play a role. Other barriers that explain variability in standard of care are for example lack of time and lack of (financial) resources. Supporting patients in adhering to medication is a complex job and implementing supportive action in pharmacist is equally difficult. Even a telephone intervention that seems relatively easy at first can be hampered by numerous internal and external factors. The attitude of the pharmacy team needs to be positive at the beginning; they need to have the proper knowledge, competences and time; and patients should have a positive attitude toward a pharmacist phone call and should trust their pharmacist. The extent of cooperation with the physician is important. And finally for a sustainable service in the long run there should be adequate funding.

A report of Booz&Co named strategies that can help to improve adherence (of the provider and the patient). Firstly, they suggested creating and deploying incentives for health care providers to integrate medication adherence in treatment plans, focussing on quality instead of volume. Secondly, the role of employers and social security administrations should be increased since low adherence can lead to productivity loss. Thirdly the current service and business models do not contribute and new models should be explored. And lastly, the impact of non-adherence, best practices and optimization of incentive models should be studied.

Recommendations for research

- The variation in level of pharmaceutical care between pharmacies should be studied in order to provide information about promoting and hampering factors. One example of a service that is already available in all Dutch community pharmacies is the ability of the clinical risk management system to generate signals at the moment a patient returns too late for a refill. Pharmacy practice research has to provide information how pharmacists actually respond to these signals
- Not all patients within a pharmacy receive the same level of pharmaceutical care nor is it for every patient optimal. The TelCIP trial demonstrated that men were less satisfied with standard care than women. Research should provide more information about how standard care is organized, who benefits most from standard care, and who needs additional care
- Discussing non-adherence, requires skills, time, a mind-set of both the patient and the provider and, above all, a patient-provider relationship built on mutual trust. It is unknown if the right conditions are always present in the pharmacy. Probably many patients will also need to get used to discussing adherence issues with their pharmacist. Research is needed to identify the optimal conditions for adherence interventions. Especially research should be targeted at how to promote patients to discuss adherence
- The suggested combination of methods to assess medication adherence could be helpful to identify and differentiate between types of non-adherence. The usability however should be studied and linked to for example patient beliefs about medication.
- Moreover, research would benefit when consensus is reached on how to use drug utilisation data for adherence research. A guideline or checklist on the reporting would be helpful
- The cluster design used in the TelCIP trial is useful to study pharmaceutical care in the 'real-world'. With this pragmatic approach multiple subgroups can be studied in one trial providing an answer for which group the intervention works best

Recommendations for clinical practice

Pharmacists have an excellent starting point for supporting patients in adherence in cooperation with physicians and other health care providers. But they can do a great deal more in this area than they did up to now. For some initiatives by pharmacists aimed at improving adherence, effectiveness has been assessed, however these have yet not been implemented on a large scale or the level of implementation is unknown. On the other

hand pharmacies exploit services that may improve adherence but their effectiveness has not yet been studied.

Despite all efforts to improve pharmaceutical care, there will always be patients that receive suboptimal care. Factors related to the patient, provider or system can hamper optimal care.[16] For example when patients cannot visit the pharmacy themselves, do not return for a refill, have low health literacy, have strong concerns or low necessity beliefs, or when intended care is not provided due to practical issues, time, or lack of competences. Suboptimal care has to be identified for each individual patient and appropriate action has to be taken. Here lies a role for the pharmacist, but also for the patient and the system. An example of an appropriate action can be the provision of telephone counselling at the start of therapy.

Pharmaceutical care aimed at improving adherence should contain at least the following elements:

- A patient-centred attitude with respect for the patient's decision
- Information targeted to the patient's needs and in line with the information provided by the physician (preferably a referral from the prescriber to discuss drug therapy with the pharmacist)
- Assessment of barriers hampering implementation of the agreed therapy followed by support in finding solutions in case barriers exist
- Feedback to the prescriber on the identified barriers and proposed solutions
- Close collaboration with other health care providers like physicians, nurses and home care

To provide optimal pharmaceutical care some prerequisites are essential:

- Supporting patients in medication-taking behaviour requires knowledge and skills. Moreover providers have to be able to address potential non-adherence in a correct, non-judgemental way. Feedback of recordings of patient-provider interaction can help improve skills
- Communication between physicians and pharmacists is essential in order to convey similar messages to the patient. Often, knowledge on the indication of medication is needed in order to tailor instructions to an individual patient. Take for example metoprolol, a beta-blocker that can be prescribed for diverse indications such as hypertension, arrhythmias, migraine prophylaxis, post myocardial infarction and for angina pectoris. The content of the message depends largely on the indication and thus knowing the indication is essential to deliver optimal pharmaceutical care
- Hampering and stimulating factors in the health care system should also be reviewed. For example generic substitution clearly has great savings for the health care budget,

but also puts pressure on the patient-pharmacist relation and moreover, for some patients it can be very confusing when the appearance of medication changes. Furthermore, the health care system should support health care providers with incentives for example by introducing remuneration for adherence interventions

- Pharmacists should have wider access to solutions that help in selecting potential non-adherent patients and monitor behaviour
- New technologies can be used to complement the work of the health care provider. For example by using applications for smart phones, patient portals, websites or reminder devices
- The patient should be supported in taking responsibility for their own health and self-management

Three idea's to improve pharmaceutical care:

1. Standard care should be that at the first interaction in the pharmacy, a patient receives sufficient information and counselling. When this is not possible or not sufficient for example when the patient expresses concerns that require additional counselling or when the patient is not visiting the pharmacy in person, the patient is contacted by the pharmacist to provide additional counselling, targeted to the patients' needs
2. For optimal counselling, experience and knowledge of the health care provider is required. In Dutch community pharmacies most interactions at the counter are between the patient and a technician. Telephone counselling can be used to improve this. For example by assigning a technician to a limited number of medication classes. Technicians can receive specific training for these medication classes. Furthermore calls can be recorded aimed at giving feedback to the technician. In this way the expertise of the technician can be improved which may also affect interactions at the counter.
3. The nature and organization of the current practice does not respect a patient's autonomy to reject a treatment. Discontinuation of therapy is highest in the first period and some patients do not even pick up the first prescription. Presumably a part of these patients did not agree with the treatment in the first place. Prescribing medication before the patient agrees with the treatment is doing things in the wrong order. For non-acute problems, it can be an alternative to first provide information to the patient, to support the patient during the decision-making process, in order to eventually make a shared decision during a follow-up appointment.

Conclusions

Supporting patients in medication adherence starts when the physician prescribes a new medicine. Many decisive moments follow the initial prescription. The pharmacist has excellent opportunities to offer further adherence support, not only the first time the patient visits the pharmacy, but also at every consecutive refill. A more proactive role focussing on patients not returning or returning too late for a refill can be helpful. Pharmaceutical care should be targeted at a patient's knowledge, concerns, necessity beliefs, and practical barriers for medication intake. This thesis demonstrates that pharmacists have ample opportunities to improve medication adherence. The pharmacist should further extend this role in counselling patients and helping them to make a shared decision. Innovative services like telephone counselling and monitoring adherence are needed to deliver full support to all patients. In the near future multimedia may offer additional solutions. The health care system should support health care providers including pharmacists in promoting medication adherence. Attention for medication-taking behaviour should be incorporated in the treatment process and in guidelines. Health care providers including pharmacists and physicians should cooperate on this subject. It is time that pharmacists take up the challenge to expand their role in promoting and supporting medication adherence.

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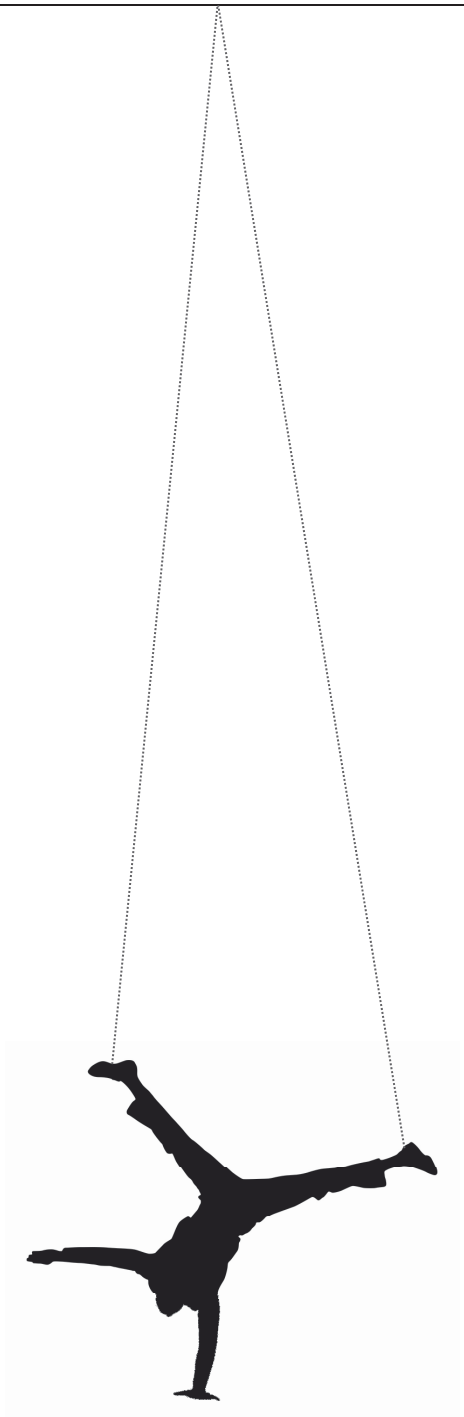
Appendix

Table 1: Domains illustrating the extremes of explanatory and pragmatic approaches to each domain (adapted from Thorpe et al.[28]).

Domain	Pragmatic trial	Explanatory trial
Participant eligibility criteria	All participants who have the condition of interest are enrolled	Selection of high risk patients, likely to respond and show high compliance
Flexibility of intervention	Instructions on how to apply are highly flexible	Inflexible. Strict instructions for every element
Provider expertise (intervention)	Full range of providers and practices	Selection of highly compliant and experienced providers and practices
Provider expertise (comparison)	Full range of providers, regardless of expertise with only ordinary attention to their training, experience and performance	Expertise is standardized
Flexibility of comparison intervention	Usual care or best available alternative	Placebo as comparator
Primary trial outcome	Objectively measured, clinical meaningful outcome. Assessed under usual conditions; no special tests required	Often clinical meaningful, but sometimes a surrogate marker of another downstream outcome of interest. Might also require specialized training or tests
Participant compliance with 'prescribed' intervention	There is no unobtrusive (or no) measurement of compliance. No special strategies to maintain or improve compliance are used	Participants compliance is monitored closely and may be pre-requisite
Provider adherence to study protocol	There is no unobtrusive (or no) measurement of compliance. No special strategies to maintain or improve compliance are used	Close monitoring of how well participating clinicians and centres are adhering
Primary analysis of outcomes	All patients are included regardless of compliance, eligibility and others (intention-to-treat analysis)	Both intention-to-treat as per-protocol analysis are performed or an analysis to 'compliers' or other subgroups
Follow-up intensity	No formal follow-up visits. Instead, use of administrative databases	Study individuals followed with many more frequent visits than would occur in routine practice



SUMMARY

Introduction

Adherence is defined by the World Health Organization (WHO) as "the extent to which a person's behaviour - taking medication - corresponds with agreed recommendations from a health care provider". Adherence to medication has in general been reported to be low. Non-adherence to medication therapy, both long-term and short term, severely compromises the effectiveness of treatment and is critical both from the perspective of individual patients and public health and health economics. Given the crucial role of medication adherence, interventions are needed that are effective and feasible to implement in daily practice.

In the introduction of this thesis (**Chapter 1**), factors associated with non-adherence were discussed including the categorization by the WHO in five dimensions: socio-economic related factors, health care team and system-related factors, condition-related factors, therapy-related factors and patient-related factors. Moreover, beliefs about medicines and both practical and perceptual barriers that hamper adherence were discussed. Three domains in improving adherence are important: the patient, the health care provider and the health care system. A helpful model to guide providers to help improve adherence is the Information-Motivation-Strategy model, stressing the importance of providing information, motivating patients and supporting to find a strategy that can be implemented by the patient.

Despite the importance of adherence, usual care is not yet optimal. Pharmacists play an important role in improving appropriate use of medication. The overall aim of this thesis was to design and evaluate interventions in community pharmacies focussing on improving medication adherence both at the start of therapy and in the implementation phase. Moreover the objective was to provide insight in the frequency and nature of counselling in pharmacies and to propose standardization for assessing medication adherence using pharmacy dispensing data.

Counselling in Dutch pharmacies

Chapter 2 provided insight in the frequency and nature of counselling in Dutch pharmacies. We defined personal consultations as contacts between a patient and a pharmacist with a pharmacotherapy related subject (i.e. not about issues such as prices of medicines) and with adequate protection of privacy (i.e. contact in a private room, by telephone or e-mail). Questionnaires were sent to 800 randomly selected community pharmacies and 198 (24.8%) pharmacies responded. The pharmacists provided an average of slightly more than one personal consultation each working day. The vast majority of respondents provided face-to-face and telephone consultations (94.4% and 91.9%, respectively) and a minority gave consultations by e-mail (30.8%). These consultations

primarily dealt with topics related to medication safety, side effects and interactions with other medicines. The average number of personal consultations was significantly associated with the absolute number of full-time equivalent pharmacists in the pharmacy. On average a private consult lasted 15.9 minutes (excluding preparation time) and counselling by telephone 7.4 minutes. The frequency of consultations in private was low at the time of the study (2004), but is likely to have increased by new services such as medication reviews that have recently been introduced.

Using dispensing data to assess medication adherence

Pharmacy dispensing data can be used to assess medication adherence. Harmonization of standards, as well as definitions of distinct measures and their operationalization to quantify adherence to medication were proposed in **Chapter 3**. Group discussions and a consensus process were used. We harmonized the concepts of adherence measures within the taxonomy as suggested by Vrijens et al. and proposed the standards necessary for the operationalization of adherence measures. Besides using a proportion to measure the extent of implementation of the drug regimen and a time-to value for the persistence with treatment, we proposed to add a dichotomous value for the re-initiation of treatment. We listed the methodological issues that should be disclosed in studies on adherence. We discussed the possible impact of the measures in adherence research. We anticipate that results of future adherence research gain in accuracy and studies will become more transparent, enabling comparison between studies.

Telephone Counselling Intervention by Pharmacists

An important part of this thesis described the Telephone Counselling Intervention by Pharmacists (TelCIP) trial (**Chapter 4**).

The design of the trial is described in **Chapter 4.1**. The TelCIP trial was a cluster randomized controlled intervention trial where pharmacies were randomly assigned to one of two groups. Each group had an intervention arm and a usual care arm. In the first group the intervention was delivered to patients starting with antidepressants or bisphosphonates and usual care was provided to patients starting with lipid-lowering drugs or Renin Angiotensin System (RAS)-inhibitors. In the second group this was the other way around: the intervention was delivered to patients starting with lipid-lowering drugs or RAS-inhibitors and usual care to patients starting with antidepressants and bisphosphonates. The intervention consisted of a structured telephone call by a pharmacist 7 to 21 days after a new prescription. The call was supported with an interview protocol. Primary aim of this call was to improve adherence by addressing the need for information, actual medication intake behaviour, practical barriers (e.g. side effects) and

perceptual barriers (e.g. concerns or low necessity beliefs). A sample of pharmacies sent questionnaires to patients, three months after the first prescription. The primary outcome measure was medication adherence assessed using dispensing records retrieved 12 months after the intervention. Patients' beliefs on medication, perception of the quality of information received and pharmacy counselling were secondary outcomes. By measuring satisfaction with information and counselling and beliefs about medication the study was designed to give insight in possible mechanisms of a potential increase in adherence.

Chapter 4.2 provided information on implementation of the TelCIP-trial. In order to interpret the effects of a multi-centre behavioural intervention, it is necessary to enhance the likelihood of consistent implementation and to monitor the actual execution of the intervention (treatment fidelity). To improve treatment fidelity, activities and strategies on different domains can be used, both in the design of the study and in the delivery of the intervention. The Behaviour Change Consortium (BCC) treatment fidelity framework of the National Institutes of Health was used to assess treatment fidelity. The framework addresses strategies on five domains: 1) study design; 2) provider training; 3) delivery of treatment (intervention); 4) receipt of treatment and 5) enactment of treatment skills. The presence and implementation of strategies in the TelCIP trial on these domains was assessed using the trial protocol, pharmacy dispensing data and pharmacists' self-reports. Treatment fidelity was high for the study design as most of the suggested strategies in the BCC framework were implemented. On the domain of provider training not all suggested strategies were implemented: no characteristics were described a priori with regard to provider training and skill acquisition was not assessed. Fidelity on delivery of the intervention was high as most delivery strategies mentioned in the framework were implemented, e.g. in 80% of the calls all knowledge items from the interview protocol were discussed and in 66.6% of the calls, important barriers from the interview protocol have been discussed. There was evidence of fidelity on receipt of treatment but enactment of treatment skills was not assessed. Overall, evidence was found for sufficient treatment fidelity of the TelCIP trial.

This chapter also provided insight in aspects of the implementation. In total 1226 patients received the intervention, which was almost half of all eligible patients. The most important reasons for not being able to counsel the patient was the absence of a telephone number or that a patient could not be reached. Older patients were more likely to actually receive the intervention than younger patients.

How pharmacists communicated with patients in the TelCIP trial, was studied in **Chapter 4.3**. This study aimed to assess to what extent pharmacists explored adherence, practical and perceptual barriers and information needs during the call. In five pharmacies 31 telephone calls were recorded. In virtually all calls, adherence (n=27), barriers (n=27) and

the need for information (n=29) were explored at least once. Most barriers expressed by patients were practical and mostly in relation to side effects. In only seven calls the pharmacists explicitly explored the presence of perceptual barriers. About half of the patients expressed a need for information. This study provided more insight in telephone counselling by pharmacists and demonstrated that pharmacists were able to address adherence, practical barriers and need for information. Perceptual barriers were less often discussed. More attention should be given to the explicit exploration of these perceptual barriers.

The results of the intervention on patients' satisfaction with counselling, satisfaction with information and beliefs about medicines were shown in **Chapter 4.4**. The data for this study were collected using a questionnaire sent to patients three months after the start with a new medicine. This questionnaire contained items assessing patients' satisfaction with counselling and items from two standardized questionnaires: the Satisfaction with Information about Medicines Scale (SIMS) and the Beliefs about Medicines Questionnaire (BMQ). Responses of 211 patients in nine pharmacies were analysed. More intervention arm patients were satisfied with counselling (adj. odds ratio (OR) 2.2, 95% CI 1.3, 3.6). Patients with counselling were significantly more satisfied with information on four information-related items, had less concerns and less frequently had a 'sceptical' attitude towards medication (adj. OR 0.5, 95% CI 0.3, 0.9). This study demonstrated that telephone counselling by pharmacists improved satisfaction with counselling and information, and - to a lesser extent - on beliefs about medicines. Effects on most outcomes were more pronounced in men than in women. The implication for practice is that pharmacists can use counselling by telephone, but more research is needed to find out which patients benefit most.

The results of the intervention on medication adherence were presented in **Chapter 4.5**. Primary outcome was refill adherence, calculated using the modified Medication Possession Ratio (MPRm). It was assessed over one year and expressed as both a continuous and a dichotomous outcome. The cut-off for the dichotomous outcome was 80%: patients with an MRPm≥80% were considered adherent and patients with MPRm<80% as non-adherent. Secondary outcome was discontinuation of therapy within one year. In the control arms 3,627 patients were eligible and 3,094 in the intervention arms. Of the latter, 1,054 patients (34%) received the intervention. For 1,495 (48%) patients it was unknown if the intervention was delivered. For 17% of the patients the reason for not counselling the patient was registered. Overall mean adherence rates between the intervention and usual care arm were not significantly different in an intention to treat analysis (74.7% resp. 74.5%). However in the intervention arm 81.4% of the patients starting with RAS-inhibitors were adherent (refill rate ≥ 80%) compared to

74.9% in the usual care arm (OR 1.4, 95% CI 1.1, 2.0). No statistically significant differences were found for the other three classes in the intention-to-treat analyses. Comparing only patients who actually received counselling to patients in the usual care arm (per protocol analysis), the proportion adherent patients was significantly higher in the intervention arm ($p<0.05$, adj. OR 1.5, 95% CI 1.2, 1.8). The proportion adherent patients was also significantly higher in patients starting with RAS-inhibitors, lipid-lowering drugs and bisphosphonates. No effects were found for antidepressants. Conclusions of this study were that telephone counselling at start of therapy had no overall effect on adherence nor for participants starting with antidepressants. However adherence with RAS-inhibitors was statistically significant improved and the study suggested also a positive effect on adherence to lipid-lowering drugs and bisphosphonates.

Interventions for non-adherent patients

Chapter 5 presented the results of a three-armed randomized trial focussing on non-adherent patients using lipid-lowering drugs, statins. The use of statins has proven to be effective in reducing cardiovascular events and mortality. However in daily practice adherence to medication is often low and this compromises the effect of therapy. The aim of this study was to assess the effectiveness of two interventions to improve refill adherence and persistence to statin treatment in non-adherent patients. We used a multicentre, community pharmacy-based randomized controlled trial conducted in 24 pharmacies in The Netherlands, with patients with prior baseline refill adherence rates between 50 to 80%. Eligible patients of ≥ 65 years were randomly assigned to 1 of 3 groups: (1) counselling with an electronic reminder device (ERD) (n=134), (2) ERD with a written instruction (n=131) and (3) control group (n=134). Primary outcome measure was refill adherence to statin treatment in 360 days after inclusion (PDC360). Patients with a refill rate ≥ 80% were considered adherent. We also assessed the effect among predefined subgroups.

There were no relevant differences at baseline. In the counselling with ERD-arm 54 of 130 eligible patients received the counselling with ERD. In the ERD-arm, 117 of 123 eligible patients received the ERD. The proportions of adherent patients in the counselling with ERD group (69.2%) and in the ERD-only group (72.4%) were not higher compared to the control group (64.8%). In the ERD group more women using statins for secondary prevention, were adherent (86.1%) compared to the usual care group (52.6%) ($p<0.005$). In men using statins for secondary prevention, no effect of the ERD was found.

In this randomized controlled trial, we found no statistically significant improvement of refill adherence with the use of an ERD with or without counselling. However, in a subgroup of women using statins for secondary prevention, the ERD improved adherence.

General discussion

In the general discussion (**Chapter 6**) we elaborated on the results described in this thesis and placed them in a broader perspective. Also, we discussed the execution of trials in pharmacy practice. We used the PRECIS tool to describe the pragmatic or explanatory nature of trials in pharmacies in general and for the two trials described in this thesis. Thoughts and implications of using dispensing data to assess medication adherence were presented. An idea was proposed to use two calculations to describe patients' behaviour in order to target interventions at the most important reason for non-adherence.

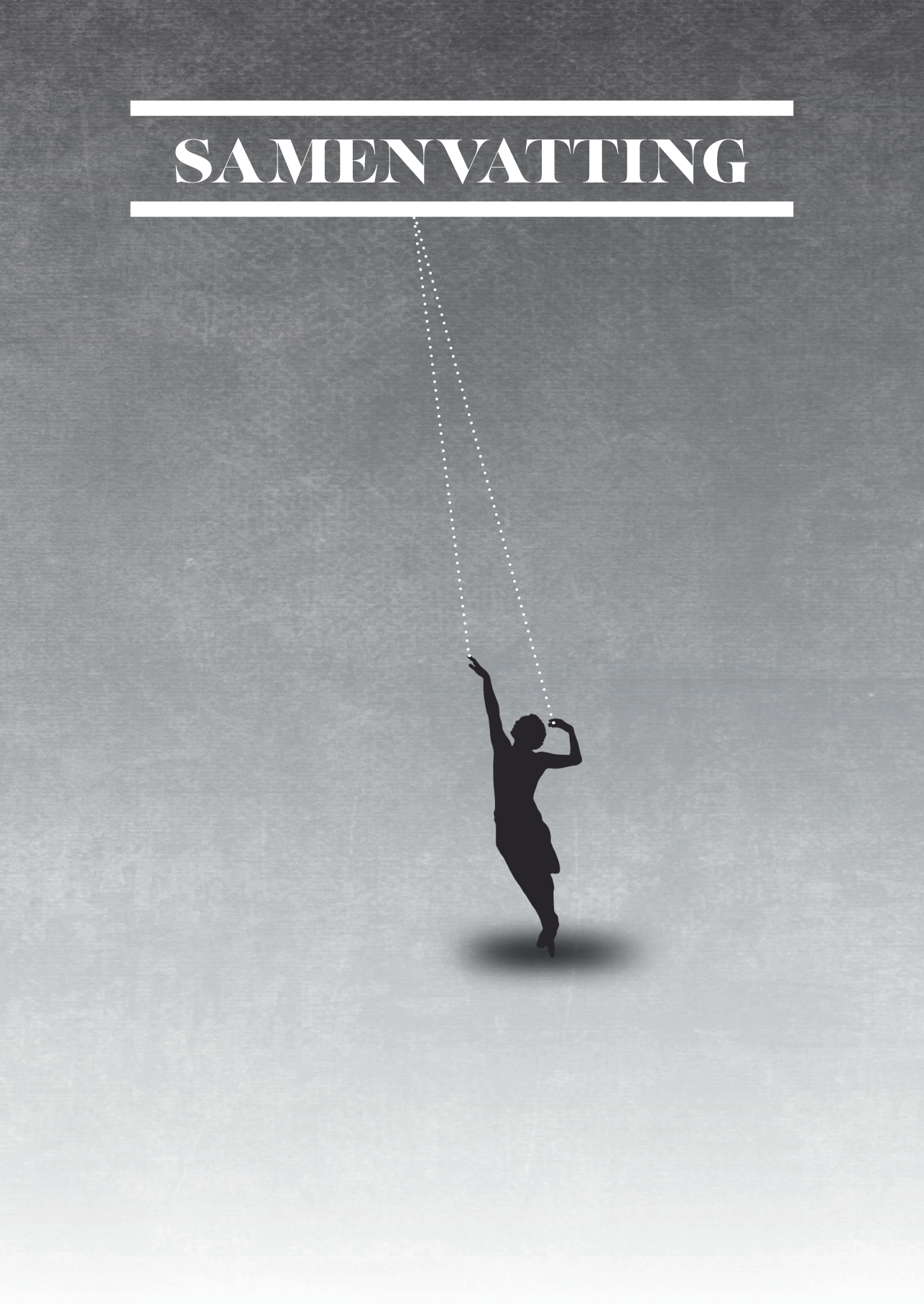
To improve adherence, standard care should be optimized and some thoughts on (pharmaceutical) care in the initiation and implementation phase of a pharmaceutical therapy were presented. The initiation phase is an important phase and health care providers should work together in this phase and support patients in making the decision whether to initiate treatment or not. In the implementation phase the pharmacists have multiple contacts with the patients and these can be used to support the patient.

Implications for research included recommendations to study variation in level of pharmaceutical care. Not only to explore promoting and hampering factors but also to know which patient benefits the most. Recommendations for clinical practice included a suggestion for essential elements of pharmaceutical care and stresses the importance of close collaboration between physicians, pharmacists, nurses and home care.

Conclusions of this thesis

Supporting patients in medication adherence starts when the physician prescribes a new medicine. Many decisive moments follow the initial prescription. The pharmacist has excellent opportunities to offer further adherence support, not only the first time the patient visits the pharmacy, but also at every consecutive refill. A more proactive role focussing on patients not returning or returning too late for a refill can be helpful. Pharmaceutical care should be targeted at a patient's knowledge, concerns, necessity beliefs and practical barriers for medication intake. This thesis demonstrates that pharmacists have ample opportunities to improve medication adherence. The pharmacist should further extend this role in counselling patients and helping them to make a shared decision. Innovative services like telephone counselling and monitoring adherence are needed to deliver full support to all patients. The health care system should support health care providers including pharmacists in promoting medication adherence. Attention for medication-taking behaviour should be incorporated in the treatment process and in guidelines. Health care providers including pharmacists and physicians should cooperate on this subject. It is time that pharmacists take up the challenge to expand their role in promoting and supporting medication adherence.

SAMENVATTING



Inleiding

Het is niet eenvoudig om geneesmiddelen op tijd en regelmatig in te nemen. Veel patiënten die voor chronische aandoeningen geneesmiddelen moeten gebruiken, hebben daar dan ook moeite mee. De Wereldgezondheidsorganisatie (WHO) heeft medicatietrouw gedefinieerd als de mate waarin het gedrag van een patiënt overeenkomt met de overeengekomen afspraken met de zorgverlener. Medicatietrouw gaat niet alleen over het al dan niet gebruiken van een geneesmiddel, maar ook of het op de juiste manier wordt gebruikt, op het juiste tijdstip en voor de juiste duur. Omdat goede medicatietrouw belangrijk is voor gezondheidsuitkomsten, zijn er veel initiatieven ontplooit om medicatietrouw te verbeteren, met wisselend succes. Sommige effectieve interventies bleken lastig in te passen in de dagelijkse praktijk. Daarom moeten interventies om medicatietrouw te verbeteren niet alleen effectief zijn, maar ook praktisch uitvoerbaar. Simpele en haalbare interventies, bij voorkeur in een omgeving waar verschillende zorgverleners samenwerken, zijn daarbij veelbelovend.

In de inleiding van dit proefschrift (**Hoofdstuk 1**) is verder ingegaan op onder meer de oorzaken van medicatieontrouw. Er zijn verschillende factoren gerelateerd aan medicatieontrouw. De WHO heeft deze factoren in vijf categorieën ingedeeld: sociaaleconomische factoren, zorgverlener en zorgsysteem gerelateerde factoren, aandoening gerelateerde factoren, therapie gerelateerde factoren en patiënt gerelateerde factoren. Hoewel de patiënt een eigen verantwoordelijkheid heeft om het geneesmiddel op de juiste manier te gebruiken, moet de zorgverlener de patiënt daarbij zoveel mogelijk ondersteunen. Zo moet de patiënt voldoende geïnformeerd en gemotiveerd worden en indien nodig praktische ondersteuning krijgen om het geneesmiddel goed te gebruiken. Niet alleen de voorschrijver, maar ook andere zorgverleners zoals apothekers, verpleegkundigen en thuiszorgmedewerkers spelen hierbij een rol. Belangrijk is ook dat zowel de patiënt als de zorgverlener hierbij ondersteund worden vanuit het gezondheidszorgsysteem, de zorgverzekeraar en de overheid.

Helaas is de zorg rondom geneesmiddelen nog niet altijd optimaal. Medicatietrouw is bijvoorbeeld zelden een onderwerp van gesprek in de spreekkamer van de huisarts. Patiënten geven ook aan onvoldoende informatie en begeleiding van de apotheker te krijgen. De apotheker en het apotheekteam hebben veel kennis over geneesmiddelen, ze zijn toegankelijk en hebben regelmatig contact met patiënten. De apotheker kan dan ook een belangrijke rol spelen bij het verbeteren van het gebruik van geneesmiddelen

Het doel van dit proefschrift was om interventies gericht op het verbeteren van medicatietrouw te ontwerpen en te evalueren in openbare apotheken. Daarnaast wilden we meer inzicht krijgen in de aard en omvang van consultvoering in apotheken en tot slot

wilden we het meten van medicatietrouw met behulp van apotheekgegevens standaardiseren.

Consultvoering in de apotheek

In **Hoofdstuk 2** staat beschreven in welke mate apothekers farmaceutische consulten voeren met patiënten. Het farmaceutisch consult hebben we gedefinieerd als een gesprek met een apotheker over geneesmiddelen (en bijvoorbeeld niet over vergoedingen) met voldoende bescherming van privacy (in een aparte spreekkamer of per telefoon of e-mail). Van de 800 willekeurig geselecteerde apotheken hebben 198 (24.8%) hierover een vragenlijst ingevuld. Ten tijde van het onderzoek (2004) voerden apothekers gemiddeld iets meer dan één farmaceutisch consult met de patiënt per dag uit. Bijna alle apothekers voerden farmaceutische consulten in een spreekkamer of per telefoon (94.4% resp. 91.9%). Een kleiner deel van de apothekers voerde e-mailconsulten (30.8%). De consulten bleken vooral te gaan over medicatieveiligheid, bijwerkingen en wisselwerkingen met andere geneesmiddelen. Gemiddeld duurde een persoonlijk 1-op-1 gesprek 15,9 minuten (exclusief voorbereiding) en een telefoongesprek 7,4 minuten. In apotheken waar meerdere apothekers werkzaam zijn, werden naar verhouding meer consulten gevoerd, ook als er rekening gehouden werd met de grootte van de apotheek. Het is al enkele jaren geleden dat dit onderzoek werd uitgevoerd. Ondertussen zijn er verschillende initiatieven ontplooid om de begeleiding door apotheken te verbeteren, zoals het voeren van medicijngesprekken met patiënten die veel geneesmiddelen gebruiken. Het is dan ook aannemelijk dat het aantal farmaceutische consulten is toegenomen.

Aflevergegevens om medicatietrouw te meten

Apothekers registeren elke medicatieverstrekking in hun systeem onder andere om te controleren of het geneesmiddel juist gedoseerd is, of het samen kan met eventuele andere geneesmiddelen en of een patiënt allergisch is. Deze aflevergegevens kunnen ook gebruikt worden om medicatietrouw in kaart te brengen. Het is bijvoorbeeld mogelijk om te signaleren of een patiënt steeds op tijd terug komt voor een herhaalrecept of dat een patiënt vaak later terug komt dan verwacht. Er bestaan verschillende methodes om met deze aflevergegevens de medicatietrouw te bepalen. Het is belangrijk dat wanneer zorgverleners en onderzoekers over het onderwerp medicatietrouw spreken, zij dezelfde taal spreken. Daarnaast is het van belang om zo goed mogelijk het gedrag van patiënten in te schatten met deze gegevens en te voorkómen dat patiënten ten onrechte worden aangemerkt als therapietrouw of juist therapieontrouw. Daarom hebben wij in **Hoofdstuk 3** voorstellen gedaan om het gebruik van deze aflevergegevens verder te standaardiseren en te harmoniseren. Bijvoorbeeld wat er gedaan kan worden als de patiënt van het ene

geneesmiddel over stapt op een ander geneesmiddel of hoe medicatietrouw berekend kan worden als de patiënt nog een voorraad heeft. Wij hebben een lijst opgesteld van aspecten die genoemd zouden moeten worden in onderzoek naar therapietrouw. Op deze manier hopen we dat studies over therapietrouw transparanter worden en dat vergelijking tussen studies beter mogelijk wordt.

Telefonische Start Begeleiding

In **Hoofdstuk 4** besteden wij aandacht aan het bevorderen van goed geneesmiddelgebruik door het invoeren van een nieuwe service bij de start van de therapie in de apotheek, de Telefonische Start Begeleiding (TSB). In **Hoofdstuk 4.1** is de opzet beschreven van dit onderzoek, de TelCIP trial. Daarbij werden vier verschillende geneesmiddelgroepen onderzocht: antidepressiva, bisfosfonaten, Renine-Angiotensine-Systeem (RAS)-remmers en cholesterolverlagers. Antidepressiva worden doorgaans gebruikt voor de behandeling van depressies of angststoornissen en bisfosfonaten voor de behandeling of preventie van osteoporose ("botontkalking"). RAS-remmers worden onder meer gebruikt voor de behandeling van hoge bloeddruk. Cholesterolverlagers worden voorgeschreven voor de behandeling van verhoogd cholesterol en voor de preventie van hart- en vaatziekten. Patiënten in de controle groep kregen de gebruikelijke zorg. Patiënten in de interventiegroep kregen de Telefonische Start Begeleiding. Daartoe belden de apotheekmedewerkers patiënten die 7 tot 21 dagen ervoor waren gestart met één van deze geneesmiddelen. Ter ondersteuning werd een gespreksprotocol gebruikt. Het doel van het gesprek was te achterhalen of er problemen waren, of de patiënt voldoende wist over het geneesmiddel en het gebruik, of de patiënt last had van bijwerkingen, of de patiënt bang was voor bijwerkingen of afhankelijkheid en of het de patiënt lukte om het goed in te nemen. Waar nodig kon de apotheker de patiënt ondersteunen, informatie geven, motiveren of verwijzen naar de voorschrijver. Het hoofddoel van het onderzoek was te bepalen wat het effect van TSB is op medicatietrouw. Daarnaast wilden we onderzoeken wat het effect was op tevredenheid en de houding die de patiënt heeft ten opzichte van het geneesmiddel. Het doel daarvan was om meer inzicht te krijgen in het mechanisme van een mogelijke verbetering van medicatietrouw.

In **Hoofdstuk 4.2** beschrijven we de uitvoering van het onderzoek in de praktijk. Om de resultaten van een onderzoek in meerdere apotheken goed te kunnen interpreteren, is het van belang om te weten of de interventie (TSB) overal uitgevoerd is zoals bedoeld door de onderzoekers. Dit wordt 'treatment fidelity' genoemd. Hiervoor hebben we een kader gebruikt van het Amerikaanse National Institutes of Health (NIH), het 'treatment fidelity framework'. Om inzicht te krijgen in de mate van 'treatment fidelity' moet volgens dit framework naar vijf domeinen worden gekeken: 1) het ontwerp van de studie, 2) de

training van de zorgverleners, 3) het uitvoeren van de interventie, 4) de mate waarin de patiënten bereikt zijn en 5) de mate waarin de patiënt zijn gedrag heeft veranderd. Om te bepalen of het onderzoek hieraan tegemoet kwam, hebben we gekeken naar het studieprotocol, de zelfrapportages van de apothekers over de uitgevoerde interventies en de aflevergegevens van apotheken. Uit de evaluatie komt naar voren dat de interventie op de meeste aspecten in grote lijnen volgens het protocol is uitgevoerd in de apotheken. De grootste onzekerheid ligt in de wijze waarop de apothekers daadwerkelijk met de patiënten hebben gecommuniceerd.

In totaal zijn 1226 patiënten gesproken. Dit is bijna de helft van alle geselecteerde patiënten. De belangrijkste reden dat patiënten niet gesproken zijn, was omdat hun telefoonnummer niet bekend was of omdat ze onbereikbaar waren. Oudere patiënten hadden een grotere kans om de interventie te krijgen dan jongere patiënten.

In bijna 80% van alle gesprekken zijn de belangrijkste vooraf gedefinieerde kennis onderwerpen met de patiënt besproken. Hierbij valt te denken aan kennis over de reden van het gebruik van het geneesmiddel of het inname advies. In twee van de drie gesprekken zijn drie belangrijke barrières om geneesmiddelen in te nemen, besproken zoals zorgen over afhankelijkheid, zorgen over bijwerkingen en zorgen over de noodzaak voor het gebruik.

In vijf apotheken zijn geluidsopnames gemaakt van 31 gevoerde TSB-gesprekken. De resultaten daarvan zijn weergegeven in **Hoofdstuk 4.3**. Het doel van dit onderzoek was om te bepalen welke onderwerpen er werden besproken tijdens de telefoongesprekken. Apothekers bleken in bijna alle gesprekken te informeren naar medicatietrouw (n=27), belemmeringen (n=27) en de informatie behoefte van de patiënt (n=29). Voornamelijk praktische belemmeringen werden geuit door de patiënt en dat betrof meestal bijwerkingen. In slechts zeven gesprekken onderzocht de apotheker uitdrukkelijk of er meer perceptuele belemmeringen waren zoals zorgen over bijwerkingen of een gebrek aan ervaren noodzaak voor het geneesmiddelgebruik. Ongeveer de helft van de patiënten bleek meer informatie nodig te hebben. Dit onderzoek heeft meer inzicht gegeven in de uitvoering van de telefoongesprekken en heeft laten zien dat apothekers in staat waren om medicatietrouw, praktische zaken en informatiebehoefte te bespreken. Het bespreken van zorgen bleek lastiger en hier is wellicht meer aandacht voor nodig.

In **Hoofdstuk 4.4** worden de resultaten besproken van de patiëntenenquête. Ongeveer drie maanden nadat de patiënt gestart was met het geneesmiddel, werd naar de patiënt een schriftelijke vragenlijst gestuurd. Deze enquête bevatte vragen uit twee gestandaardiseerde vragenlijsten, de SIMS en de BMQ. De “Satisfaction with Information about Medicines Scale” (SIMS) meet de tevredenheid over de verkregen informatie over medicijnen en de “Beliefs about Medicines Questionnaire” (BMQ) meet de houding die de

patiënt heeft tegenover het gebruik van het voorgeschreven medicijn. Daarnaast zijn er vragen opgenomen die informeerden naar de tevredenheid over de begeleiding van de apotheek. De antwoorden van 211 patiënten uit in totaal negen apotheken zijn geanalyseerd. Daaruit kwam naar voren dat patiënten in de interventiearm, tevredener waren over de begeleiding dan patiënten in de controlegroep (gecorrigeerde odds ratio [OR] 2,2; 95% BI 1,3-3,6). Gebelde patiënten waren op vier van de negen kennis items significant tevredener over de informatievoorziening dan patiënten in de controlearm. Daarnaast hadden gebelde patiënten minder zorgen over het medicijn en hadden ze minder vaak een sceptische houding tegenover het medicijn (gecorr. OR 0,5; 95% BI 0,3-0,9). Opvallend was dat de effecten van de Telefonische Start Begeleiding sterker waren bij mannen dan bij vrouwen en dat er bij vrouwen niet veel verschillen met de controlegroep te zien waren. Mannen waardeerden het telefoongesprek ook veel meer dan vrouwen.

Het primaire doel van de TelCIP-trial was het verbeteren van medicatietrouw. De resultaten hiervan zijn gepresenteerd in **Hoofdstuk 4.5**. Daarbij werd op twee manieren gekeken naar medicatietrouw: hoe regelmatig patiënten het geneesmiddel afhaalden (de afhaalratio) en of patiënten in het eerste jaar stopten met het gebruik. De afhaalratio wordt uitgedrukt als een aangepaste “Medication Possession Ratio”, de MPRm. De regelmaat van afhalen is uit te drukken in een percentage variërend van 0 tot 100%, waarbij geldt dat hoe lager het percentage, hoe meer dagen de patiënt waarschijnlijk zonder medicatie zat. Patiënten met een MRPm≥80% werden gezien als medicatietrouw en patiënten met een MPRm<80% als medicatieontrouw.

In de controlearm zijn 3.627 patiënten meegenomen in de analyse en in de interventiearm 3.094 patiënten. Van deze laatste groep, zijn uiteindelijk 1.054 patiënten (34%) daadwerkelijk gesproken door de apotheker. Van 1.495 (48%) was het onduidelijk of de patiënt wel of niet gesproken is. Alles bij elkaar genomen waren de patiënten in de interventiearm gemiddeld even medicatietrouw als patiënten in de controlearm (75,7% resp. 74,5%). Maar aangezien de aandoening en de therapie van invloed is op medicatietrouw, hebben we ook naar de vier afzonderlijke geneesmiddelgroepen gekeken en daar zagen we wel verschillen. Van de patiënten in de interventiearm die waren gestart met een RAS-remmers was 81,4% medicatietrouw (MPRm≥80%) tegenover 74,9% in de controlegroep. Dit is een significante verbetering (OR 1,4; 95% BI van 1,1-2,0). In de interventiearm bleken significant minder patiënten gestopt te zijn met de medicatie vergeleken met de controlegroep (22,6% versus 27,9%). Bij de cholesterolverlagers kwamen beide effecten ook naar voren, maar wel minder sterk en niet statistisch significant. De groep van patiënten die startten met bisfosfonaten was klein en we zagen wel een effect, maar ook dat was niet statistisch significant. Bij de antidepressiva was het

aantal patiënten veel groter, maar daar was geen effect te zien van de service: patiënten in de interventiegroep haalden hun geneesmiddelen even (on)regelmatig als controle patiënten en stopten even vaak en snel. Van een deel van de patiënten die gebeld hadden moeten worden, is onbekend of ze gebeld zijn. Deze patiënten zijn boven wel meegenomen in de analyses. In een aanvullende analyse hebben we deze echter uitgesloten en hebben we alleen de patiënten die daadwerkelijk gebeld zijn vergeleken met de patiënten in de controle arm (per-protocol analyse). Gecorrigeerd voor een aantal factoren waren de gebelde patiënten significant vaker medicatietrouw (OR 1.5; 95% BI 1,2-1,8). Ook voor de RAS-remmers, cholesterolverlagers en bisfosfonaten zagen we een significante betere medicatietrouw onder gebelde patiënten dan onder controle patiënten. Alleen bij antidepressiva zagen we wederom geen effect. Telefonische Start Begeleiding blijkt daarmee effectief in het verbeteren van medicatietrouw voor RAS-remmers en lijkt ook medicatietrouw te verbeteren bij cholesterolverlagers en bisfosfonaten, maar niet bij antidepressiva.

Verbetering van medicatietrouw bij 'ontrouwe' patiënten

In **Hoofdstuk 5** zijn de resultaten van een onderzoek gepresenteerd gericht op patiënten die niet medicatietrouw waren met statines. Statines zijn de meest de meest gebruikte cholesterolverlagers en zijn effectief in het voorkomen van (verergering) van hart- en vaatziekten. Medicatietrouw met deze geneesmiddelgroep blijkt echter vaak laag. Het doel van dit onderzoek was te onderzoeken of medicatietrouw door een interventie. Voor dit onderzoek werden patiënten geselecteerd die hun medicijnen vaak te laat kwamen afhalen. In 24 apotheken werden patiënten van 65 jaar of ouder geselecteerd met een medicatietrouw ratio tussen de 50% en 80%. Patiënten werden willekeurig toegewezen aan één van drie groepen: 1) medicijngesprek met een wekker (n=134), 2) wekker met een schriftelijke instructie (n=131) en 3) aan een controlegroep (n=134). De wekker was een apparaatje dat elke dag op een ingesteld tijdstip een geluid maakt om de patiënt er aan te herinneren dat het medicijn ingenomen moest worden. Tijdens het medicijngesprek werd onder meer besproken waarom een patiënt mogelijk medicatieontrouw was.
De belangrijkste uitkomst maat was het aantal patiënten dat medicatietrouw was waarbij patiënten met een medicatietrouw ≥ 80% werden beschouwd als therapietrouw.
Het bleek moeilijk om de patiënten in de eerste groep naar de apotheek te laten komen voor een medicijngesprek: minder dan de helft ging in op de uitnodiging. Van deze groep was uiteindelijk 69,2% medicatietrouw (≥80%). In de groep die de wekker kreeg, was 72,4% medicatietrouw en in de controlegroep was 64,8% medicatietrouw. Deze verschillen waren niet significant. In een aanvullende analyse hebben we de effectiviteit in subgroepen onderzocht waarbij is gekeken naar de reden van gebruik van de statine.

Daarbij hebben we specifiek gekeken naar patiënten zonder andere relevante aandoeningen en naar patiënten met diabetes mellitus type II (suikerziekte) of een hart- en vaatziekte. Opvallend genoeg bleek het apparaatje wel duidelijk effect te hebben bij vrouwen die de statine kregen omdat ze een hart- en vaatziekte of diabetes hadden. Van deze groep was in de interventiegroep 86,1% therapietrouw vergeleken met 52,6% in de controlegroep. De reden van dit effect is niet bekend.

Algemene discussie

In **Hoofdstuk 6** beschouwen we de resultaten van de uitgevoerde onderzoeken en plaatsen we deze in een breder kader. Daarbij wordt aandacht besteed aan het opzetten en uitvoeren van praktijkonderzoek in apotheken. Ook zijn we ingegaan op het gebruik van aflevergegevens om medicatietrouw te meten. Daarbij doen we een suggestie om meerdere maten te combineren om zo specifiekere selecties van patiënten te kunnen maken en betere zorg-op-maat te kunnen leveren. Zo zal een patiënt die af en toe het medicijn vergeet iets anders nodig hebben dan een patiënt die stopt in verband met bijwerkingen.

Om medicatietrouw te verbeteren, moet de standaardzorg ook worden verbeterd. Daarom hebben we de verschillende stappen in het medicatieproces besproken en aangegeven hoe artsen en apothekers het goed gebruik van medicijnen kunnen bevorderen. Het hoofdstuk is afgesloten met aanbevelingen voor verder onderzoek en aanbevelingen voor de dagelijkse praktijk. Eén aspect daaruit is dat er meer gekeken moet worden welke patiënten extra zorg nodig hebben, bijvoorbeeld omdat ze moeite hebben met het lezen van een bijsluiter of veel zorgen hebben. Deze patiënten dienen extra aandacht te krijgen, bijvoorbeeld door het geven van Telefonische Start Begeleiding. Apothekers kunnen het medicijngebruik ook monitoren om waar nodig extra te ondersteunen. Regels van de overheid en zorgverzekeraars zouden daarbij niet moeten bijten zoals in de huidige situatie het geval is wanneer patiënten achteraf een rekening krijgen voor de informatie van de apotheek. Dit leidt er toe dat een deel van de patiënten deze informatie weigert. Daarnaast moet er ruimte komen om zorg-op-maat te kunnen leveren.

Conclusies van dit proefschrift

Het ondersteunen van patiënten bij het goed gebruik van medicijnen begint op het moment dat de arts het medicijn voorschrijft. Daarna volgen andere cruciale momenten, zoals de eerste keer dat de patiënt het medicijn ophaalt in de apotheek. De apotheker heeft veel mogelijkheden om de patiënt te ondersteunen. Niet alleen bij het eerste bezoek, maar ook elke keer als de patiënt voor een herhaalrecept komt. Een pro-actievere rol is wenselijk, bijvoorbeeld gericht op patiënten die niet terug komen voor een herhaalrecept.

De farmaceutische patiëntenzorg en de begeleiding van de apotheker zou zich moeten richten op de kennis van de patiënt, de zorgen, de overtuigingen en belemmeringen voor medicatietrouw. Dit proefschrift laat zien dat apothekers goede mogelijkheden hebben om medicatietrouw te verbeteren. De apotheker moet deze zorgverlenende rol verder uitbreiden en waar mogelijk de patiënt ondersteunen bij het maken van een weloverwogen beslissing om al dan niet te starten met het gebruik van het medicijn. Services zoals Telefonische Start Begeleiding en het monitoren van medicatietrouw zijn nodig om de patiënt te ondersteunen. Verder moet het gezondheidszorgsysteem de zorgverleners ondersteunen bij het verbeteren van medicatietrouw. Aandacht voor het gebruik van medicijnen moet onderdeel worden van de contacten tussen zorgverlener en patiënt en moet expliciet worden opgenomen in de richtlijnen. Samenwerking tussen zorgverleners inclusief apothekers en artsen rondom medicatietrouw is essentieel. Het is tijd dat apothekers de uitdaging aangaan en hun rol in het begeleiden en ondersteunen van medicatietrouw uitbreiden.

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Maar natuurlijk hadden we niet zoveel patiënten kunnen includeren zonder het enthousiasme van de individuele deelnemende Service Apotheken. De apothekers en hun team van de volgen apotheken hebben meegewerkt aan het onderzoek: Service Apotheek Malden, Apotheek van Poppel, Service Apotheek Nieuwland, Service Apotheek Rochus, Service Apotheek van Weringh, Service Apotheek Susteren, Service Apotheek De Baandert, Service Apotheek Waesbeeck, Service Apotheek Epe, Service Apotheek Blanckenburgh, Saturnus Service Apotheek, Service Apotheek Slikkerveer, Service Apotheek Bolnes, Service Apotheek Holendrecht, De Schinkel Apotheek, Service Apotheek Cuijk, Centrum Apotheek Zoetermeer, Dorpsweg Service Apotheek, Service Apotheek St. Willibrord, Vesting Service Apotheek, Huygens Service Apotheek, Service Apotheek Brusse, Service Apotheek Nieuw Gastel, Service Apotheek Oudenbosch, Service Apotheek ter Aar, Service Apotheek Van der Sluis, Zuiderpark Service Apotheek, Service Apotheek Maar, Zuiderapotheek en Service Apotheek Staatslieden en natuurlijk Service Apotheek Koning. Allen hartelijk bedankt! Zonder jullie was het niet gelukt.
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Een aantal stage apotheken hebben toestemming gegeven om de apothekers-in-opleiding ook patiënten te laten includeren voor het TSB-onderzoek: Hoogravense Apotheek
Boots Apotheek Houten, Zuilense Apotheek, Kring-Apotheek Kuylman, Apotheek Zwaaiplein, Apotheek Ex Aqua, Kring-Apotheek Kromme Rijn, Apotheek Bilthoven, Service Apotheek Zenderpark, Mediq Apotheek Overkapel, Apotheek Oog in Al, Apotheek Dr. F. Amelink, Escura Apotheek Reigerhof, Service Apotheek Ramleh, Apotheek Groesbeek, Apotheek Zorgvlied, Apotheek Stevenshof, Boots Apotheek Ziekenzorg, Apotheek Archipel, Leerdamse Service Apotheek, Thorbecke Apotheek, Apotheek GZC Orion, Service Apotheek Westwijk. Daarvoor mijn hartelijke dank.

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Dear Isabelle Arnet, the singing presenter. You are also one of the interesting people I have met during the Espacomp meetings. In the summer of 2014 you spent a couple of weeks in Utrecht and we worked together on dispensing data. I really enjoyed the sessions together. Merci beaucoup! Maybe next time in Basel?

Collega's van de afdeling Farmacoepidemiologie en klinische farmacologie van de Universiteit Utrecht ben ik dankbaar voor hun al dan niet indirecte bijdrage. Anja, Ineke en Suzanne van het secretariaat, bedankt voor jullie hartelijkheid en het soepel laten verlopen van aanvragen en logistieke zaken. Dr. Patrick Souverein bedankt voor je bijdrage aan het ERD onderzoek en je hulp bij de therapietrouwberekeningen. Dr. Svetlana Belitser heel hartelijk dank voor het uitvoeren van de multilevelanalyses en het meedenken.
Hoewel ik niet heel vaak op de universiteit was, voelde ik me er wel erg welkom., dank daarvoor. And in English: Although I didn't visit the university often, I did feel very welcome and I want to thank all my colleagues of Pharmacoepidemiology and Clinical Pharmacology for their enthusiasm: Corinne, Niels, Rik, Maarten, Hilda, Susanne, Sander, Rianne, Talitha, Sani, Yaser, Jamal, Soulmaz, Alfi and Hamid. Heshu Abdullah, regelmatig hebben we leuke discussies gevoerd tijdens de lunch of bij het koffiezetapparaat. Ook al waren we beide erg druk door de combinatie van praktijk en onderzoek, toch hebben regelmatig even een momentje gevonden. Ik waardeerde dat zeer en mis je op de UU. Fatma Karapinar, dank voor je opbeurende woorden en je handige tips! Jacqueline van Paassen en Majanne Wolters, bedankt voor jullie input bij het opzetten van het

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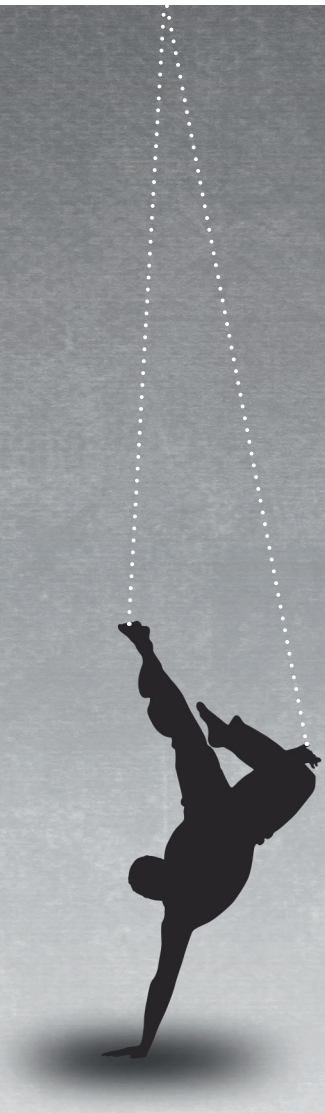
LIST OF PUBLICATIONS



Publications related to this thesis

Kooy MJ, Dessing WS, Kroodsma EF, Smits SR, Fietjé EH, Kruijtbosch M, et al. Frequency, nature and determinants of pharmaceutical consultations provided in private by Dutch community pharmacists. Pharm World Sci 2007;29:81-9.

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Registratie ontslagmedicatie in de regio Amsterdam: overdracht medicatiegegevens nog verre van ideaal. Janssen MJA, van Breukelen RL, Borgsteede SD, Kooy MJ, Karapinar-Çarkıt F. PW Wetenschappelijk Platform. 2011;5:a1126

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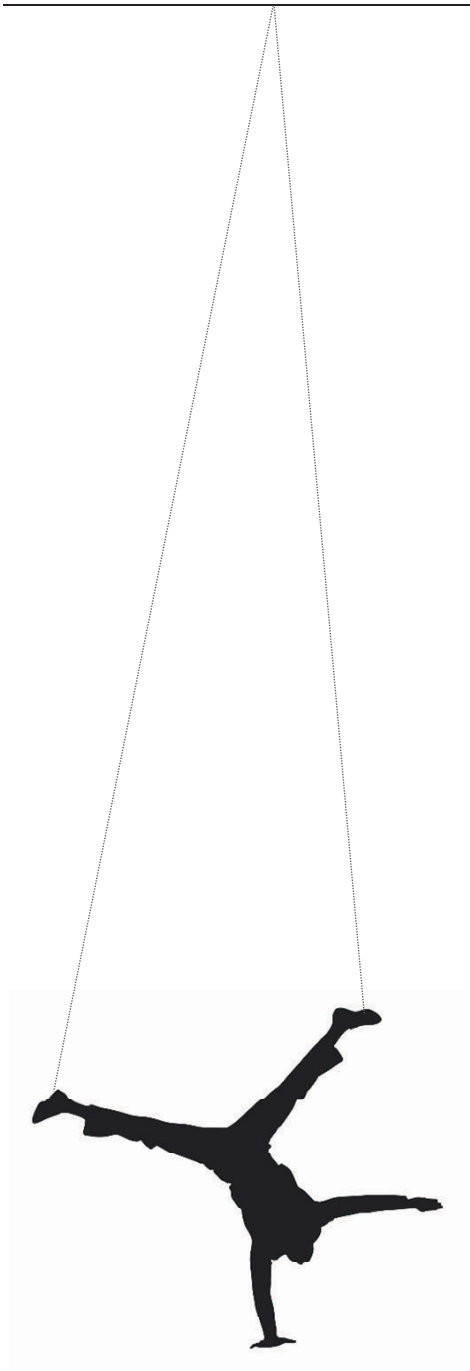

Marcel Kooij was born in 1978 in Enschede, the Netherlands. After his graduation in 1996 from the Ichthus College, he studied pharmacy at the Rijksuniversiteit Groningen. During his study he worked as student assistant in the bachelor and master phase. During his master he participated in research at the department of Pharmacokinetics and Drug Delivery focussing on drug targeting. In 2003 he received his Master of Science degree in Pharmacy with the specialization Pharmacokinetics and Drug Delivery. After his graduation he started working at Service Apotheek Koning in Amsterdam. This pharmacy is part of a modern healthcare centre, together with general practitioners and specialists. In 2004 he finished a masterclass in Pharmacy Practice Research at the SIR Institute for Pharmacy Practice and Policy. In 2005-2007 he combined his work in the community pharmacy with a position at the scientific department of the Royal Dutch Pharmaceutical Society (KNMP) and the Foundation for Pharmaceutical Statistics (SFK) where he worked on identification of suboptimal and inadequately treated patients, based on dispensing data. In 2008 he initiated a project focussing on medication reviews which resulted in the invention and development of the MedicationReviewTool.
In his work as a community pharmacist he frequently came in contact with patients having difficulty with adhering to the treatment. This motivated him to initiate this thesis in 2010 (alongside his work in the pharmacy) with the main objective: how can pharmacists support patients in adhering to the agreed treatment? As part of his PhD training he followed courses on epidemiology organised by EpidM, VuMC. He presented results of his thesis at both national and international conferences: Prisma 2010, 2013, 2014 and 2015, FIP 2012, EspaCOMP 2012, 2013 and 2014 and ESCP 2012.

Besides his work in the pharmacy and at the university, he is actively involved in several boards and committees focussing on improvement of the quality of pharmaceutical care and improvement of collaboration between health care professionals. In the region of Amsterdam, he is a board member of Stichting Ozis Amsterdam (SOZA) (since 2004), of Stichting Elektronisch Zorgdossier Amsterdam (EZDA) (from 2010 till 2014), of Farmaceutisch Bureau Amsterdam (since 2015) and of SIGRA (since 2015). He also wrote columns for the Dutch pharmaceutical journal, 'het Pharmaceutisch Weekblad'.
Since 2015 he is a board member of the Wetenschappelijke sectie Openbaar Apothekers (WSO) of the KNMP in The Hague. He is also a board member of the scientific committee of WP (Wetenschappelijk Platform), the Dutch scientific journal for pharmacists.

Central theme in all his pharmacy related activities is his passion to help patients by improving both pharmaceutical care and the communication and cooperation between different health care providers.