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Improving medication safety in the elderly

een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

Proefschrift

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CONTENTS

Chapter 1

Introduction

Introduction

This introduction describes a number of topics related to medication safety for the elderly and it gives an overview of the literature concerning these subjects. It also provides an outline of the studies we performed in our research project with the aim to improve medication safety in the elderly.

Medication safety

Patient safety is a relevant topic since the publication of the report ”To err is Human” of the Institute Of Medicine[1]. This report showed that the health care system in the United States is not as safe as it should be, and gives recommendations for improvement. Patients die or suffer from harm because of medical errors that could have been prevented. Besides the personal harm as caused by these medical errors they are associated with high health-care expenditures. The report indicated that human failure is responsible for a number of medical errors, but high numbers of problems are related to faulty systems and processes that enhance the risk at medical errors. Although it is impossible to prevent human failure, it seems wise to look carefully at the systems and processes and optimise them to minimise the risk at medical errors[1].

Studies have shown that improvement can be made in patient safety in the Netherlands too. In a study aimed at unintentional harm in Dutch hospitals the medical records of 7926 patients admitted to 21 hospitals were investigated. One of the conclusions of this study was that about 10.000 patients in the Netherlands were suffering from continuing unintentional harm caused by medical errors, in about 40 percent of the patients this harm could have been prevented. This study showed also that the elderly are especially at risk at medical errors. Furthermore it seemed that in about 30 percent of the preventable medical errors medication was included[2].

When patient safety is narrowed to the safe use of medicines the term medication safety is used. This term is defined as freedom of actual injury during the course of medication use. It includes activities to avoid, prevent or correct adverse drug events which may result from the use of medications [3].

A study of the Health Care Expectorate aimed at safe use of medicines and medical devices in the Netherlands showed that elderly are too often prescribed harmful drugs or combinations of drugs, too little attention is devoted to the specific characteristics of this group when prescribing medicines[4]. Two recent studies of medication related hospital admission in the Netherlands showed that elderly are especially at risk for medication related hospital admissions[5,6]. These studies indicate that improvement can be made in medication safety in the Netherlands and that special attention should be paid to the group of elderly drug users.

Medication safety and geriatric prescribing

The sensitivity of the elderly to medication related problems is partly caused by physiological changes related to ageing. Both the incidence and the manifestation of drug toxicity are different in the elderly when compared to younger individuals. The ability to excrete and metabolise medications, the distribution of drugs over body compartments, and the organ sensitivity to medicines all change with ageing. Elderly do experience difficulties in taking medicines as prescribed, because of problems with coordination, vision, hearing and cognition. Table 1 gives an overview of the problems, the underlying mechanisms and some examples of medicines of which the effectiveness is affected by ageing.

Although the body functions in elderly generally decline there is a large variability within this population. For some elderly there are almost no signs of ageing, while for others, especially when suffering from a number of diseases, ageing is apparent. As the response to normal dosages of medicines is unpredictable medicines should be started in low dosages in an elderly population, depending on the effect of the medicine the dosage can then be adjusted until the desired effect is reached (Start low and go slow)[7-9].

Table 1 Overview of functions that are influenced by ageing with examples of medicines being affected [7,8,10-12]

	Mechanism	Examples
Renal function	Glomerulosclerosis and decrease of renal blood-flow, both leading to a decline in clearance	Digoxin Lithium
Hepatic function	Decrease of hepatic blood-flow causing a decline in first pass metabolism resulting in higher plasma levels.	Morphine Propranolol
Drug distribution	Body water contents declines (causing high plasma concentrations of hydrophilic medicines, especially when diuretics are used) Body fat increases (causing higher half life times for hydrophobic drugs)	Lithium Aspirin Flurazepam Diazepam
Pharmacodynamic changes	Many organs have altered sensitivity to medications even at normal drugs concentrations	Beta-blocking agents
Vision	Problems reading labels and written information	All medicines
Hearing	Problems hearing verbal instruction from general practitioner and pharmacy-assistant	All medicines
Coordination	Problems opening packages and administration of complicated administration forms	Inhalation medicines Eye drops
Cognition	Problems in taking the right medicine at the right time (getting especially complicated when using more medicines)	All medicines
Depression	Depression gives decreased adherence to pharmacotherapy, elderly have an increased risk of depression	All medicines

To study and improve prescribing for the elderly various criteria for (inappropriate) geriatric prescribing have been published. A well-known example of such criteria is the Beers list, consisting of medicines that should not be prescribed for geriatric patients [13]. In an updated version of this list drug-disease interactions that are especially important for the elderly are included [14]. A number of researchers did use this list or modifications of this list

to study inappropriate prescribing in the elderly. Percentages of patients using at least one drug of the Beers list ranged from 10-38% [15-19].

In other studies different criteria were developed to study inappropriate prescribing for the elderly such as the Medication Appropriateness Index (MAI [20,21]). In this index a number of implicit criteria are included, like indication, effectiveness, dosage, drug-drug and drug-disease interactions, therapeutic duplication, duration of therapy, costs of the therapy and correct en practical directions for the patient. In studies using these criteria improvements were needed in about 40% of all medicines[22].

Another example are the ACOVE quality indicators for "Assessing Care Of Vulnerable Elders". These ACOVE indicators concern a number of conditions from which elderly are frequently suffering. Medication use in the elderly has its own ACOVE indicators, most of which aim at good monitoring practice. Furthermore, a number of explicit criteria are posed (when a hypoglycaemic drug is indicated, then chlorpropamide should not be used)[23,24].

Polypharmacy

Literally, polypharmacy means using more than one medicine at the same time. In the literature the term polypharmacy generally is used when a substantial number of medicines is used by a patient in a specific period of time, although no official definition exists that includes a specific number of medicines. Another definition for polypharmacy is using too many medicines, for example, medicines with no clear indication or medicines used to treat side-effects caused by another drug. This last example is known as the prescribing cascade; e.g. amlodipine causes oedema, which is treated with hydrochlorothiazide, causing hypokalemia which is treated with potassium supplements, causing stomach problems which is treated with protonpump inhibitors etc.

It seems particularly important to deal critically with polypharmacy in elderly patients because this causes different types of problems and is responsible for high health care expenses.

Prevalence in the elderly

When people are ageing the number of chronic conditions increases, so ageing will lead to an increase in the use of medicines for chronic diseases. Furthermore, substantial numbers of preventive medicines have been developed and they take their places in prescription/treatment guidelines. Evidence is increasing that such therapies are also useful in the elderly, e.g. statin therapy [25,26], so treatment of chronic diseases in the elderly requires an increasing number of drugs.

The prevalence of medication use among the ambulatory population increases substantially with advancing age. In the Netherlands the annual number of prescriptions for the elderly of 65 or over is almost 3 times higher than that for the Dutch population on average, the number of prescriptions delivered for elderly of 75 years or over is even four times higher (35.9 prescriptions/year versus 8.9 prescriptions/year). About 80% of all prescriptions for the elderly of 65 years or over are repeat prescriptions. On average this group uses three different medicines daily[27]. In Dutch studies considering polypharmacy in the elderly in primary care comparable amounts of medicines have been found [28-30].

Elderly use relatively cheap medicines, but they do use a high volume, which leads to high costs. The elderly of 65 years and older comprise only 14% of the population but are responsible for 40 % of medicine costs. For the elderly of 65-74 years the medicine costs are about 2,5 times higher than for the Dutch population on average (658 Euro a year versus 270 euros), for the elderly of 75 years or over these costs are even 3.3 times as high (890 Euros a year versus 270 euros)[27]. Furthermore ageing of the population will lead to an further increase in medicine costs. In 2006 14% of the population in the Netherlands was 65 years or over, this percentage of elderly is bound to increase to 15% in 2010 and 19% in 2020 [31], leading to a supplemental increase in the costs related to medicines of 26 million Euro yearly[27].

Polypharmacy and user-related problems

Polypharmacy increases the risk of confusion about the practical intake of medicines, especially in the elderly with deterioration in cognition, vision or coordination. Because of decreased muscle strength and problems with coordination elderly can have practical problems when taking their medicines. These problems can emerge when using complicated dosage forms, like inhalation devices [32-34] or eye drops [35,36]. Some other studies address problems with breaking tablets [37,38] and handling medicine packages [39].

On the other hand managing complicated medication regimens can also lead to problems, patients do not know when to take what kind of medicine. Especially when cognition is decreasing the management of the increasing number of medicines becomes a problem. Even more problems may be expected when medication changes are made by the prescriber, when branded medicines are replaced by generic medicines or in case of switches between generic labels (leading to tablets with other colours and shapes). Patients may get confused and continue the medicine that is supposed to be stopped or take both the branded medicine and the generic one. These problems may result in unintentional under- or overuse with the consequence that the patient does not receive full benefit of treatment or may suffer from side effects.

Numerous studies address non-adherence [40-44], which can be divided into intentional and unintentional non-adherence. These kinds of non-adherence are two very distinctive problem areas that should be handled by means of different types of interventions. To reduce intentional non-adherence motivational interventions can be offered, whereas interventions aimed at education and training can be offered to reduce unintentional non adherence.

Polypharmacy and prescribing

The recognition that most common conditions regularly have to be treated with more than one agent (e.g. diabetes mellitus, angina pectoris) has led to obligatory or rational polypharmacy. This concept has shifted the focus on polypharmacy in recent years from reducing the number of medicines to optimizing pharmacotherapy[45]. Although polypharmacy increases a number of risks, like the occurrence of adverse drug reactions and hospitalisation, medicines that are necessary for optimal treatment of the conditions the patient suffers from should be considered. The risk of unavoidable adverse drug reactions should be weighed against the knowledge that dose-related failure of existing therapy to manage the condition may be one of the most important drug-related reasons for admission of the elderly to hospital [46,47]. Therefore the benefit-risk ratio should be assessed more thoroughly in the elderly using higher numbers of medicines than in younger patients using no co-medication.

Nowadays more and more attention is paid to disease management programs. In these the presence of singular co-morbidities is often indicated but the presence of multiple morbidities, as frequently seen in the elderly, is mostly not addressed. When blindly following treatment guidelines conflicting recommendations and drug-drug or drug-disease interactions can emerge. Especially when a number of chronic conditions are present, healthcare professionals should balance and prioritize medication use, and an individual health-care program should be made for each geriatric patient with multimorbidity [48].

Patients with a short life expectancy will not benefit from the preventive effects of medicines like statins. Holmes has proposed a model that includes four components that can be used to balance the pros and cons of prescribing (or discontinuing) medications in the elderly. The components included in this model are remaining life expectancy, time until benefit, goals of care and treatment target [49].

Polypharmacy as a risk factor

The incidence of adverse drug reactions increases with the number of medications taken [50-52]. The link between polypharmacy and the risk of drug-related hospitalisation seems clear when considering that polypharmacy increases non-adherence, adverse drug reactions and

drug-drug interactions. Some studies have shown that this is associated with the number of drugs used [5,51-54]. In a number of studies higher age was also related to an increased risk of drug-induced hospital admission [5,6,52,55]. In a literature review evaluating the incidence of adverse patient outcomes due to drug-drug interactions it was found that interactions were held responsible for 4.8% of the hospital admissions for the elderly (> 65 years), while this percentage in the whole population was only 0.57%[56].

A number of studies have shown that only a small number of drug classes are responsible for a high proportion of drug-related hospital admissions. A recent systematic review found that antiplatelets, diuretics, NSAIDs, and anticoagulants were responsible for more than half of all drug-related hospitalisations [54]. Other studies also indicate digoxin, calcium channel blockers, antidiabetics, corticosteroids and psycholeptica, cytostatics and immunosuppressives[5,6,52,55,56]. These drugs associated with high proportions of drug-related problems are drugs that are commonly used by the elderly.

Medication review

Periodical review of pharmacotherapy

In The Netherlands all prescriptions for outpatients are checked in daily routine by the pharmacy computer. When a medicine is added that leads to a direct problem a signal will warn the pharmacy-assistant (for example in case of drug-drug interactions, drug-disease interactions, dose-changes etc). In some instances no direct problems will emerge when delivering a medicine although it is not the most elegant solution of the problems as presented to the GP (e.g. prescribing a second medicine for treatment of a side effect instead of changing the medicine causing the problem, if possible), in other instances no signals are generated by pharmacy-systems yet (e.g. geriatric dosages or duration of therapy). Other problems can be identified more easily by looking at a graphical representation of the whole pharmacy record and may remain undetected in daily routine (for example a medicine that is stopped without a logical substitute).

By means of a periodical review of complete pharmacotherapy of a specific patient, problems that otherwise would go unnoticed, can be identified and feedback can be given to the GP. In these reviews a pharmacist searches for problems or improvements needed, e.g. are all diseases treated following guidelines, do all medicines used have a proper indication, are the medicines suitable for this specific patient (considering age, and possible other diseases). Literature has shown that reviewing the complete pharmacotherapy results in positive effects, such as a decrease in inappropriate prescribing score, higher percentages of problems solved or more medication changes in the intervention group compared to the control group [22,57-59].

Periodical reviews can be performed based on explicit or implicit criteria. An example of explicit criteria for treatment review concerning the elderly are the Beers criteria [13]. Explicit criteria can be used by less experienced persons, they only have to keep in mind the list of medicines that should not be used by the elderly or not used by the elderly suffering from certain conditions. These criteria can also be used to build a computerised screening tool.

Implicit criteria, on the other hand, are based on the clinical judgement of the reviewing healthcare professional. Specific information about the health condition of the patient should be used to weigh up the pros and cons of certain drug therapies. As explicit and implicit criteria have their own benefits and limitations, a combined application may offer a more thorough assessment than each approach separately[60].

Private pharmaceutical consultations

Medication reviews involving direct contact with the patient (also known as private pharmaceutical consultations, medicines consultations etc) can be used to solve (or prevent) user-related and prescription-related pharmaceutical care issues. The patient is either asked to visit the pharmacy or general practice with all medicines he/she uses, or the medication review is performed at the home of the patient. Firstly, the patient is asked whether he/she has problems with the use of medicines, and whether side effects are experienced. Subsequently a number of questions are asked for each medicine (about daily dosage regimen, the reason for using the medicine, what to do if a dosage is missed etc.). Furthermore, the patient is asked which non-prescription drugs are used to check whether they can be taken in combination with the prescription medicines.

Studies have shown that the number of user-related pharmaceutical care issues decreases after such reviews[58,61,62]. Although not all studies indicate an effect at adherence, some studies have shown improved knowledge and adherence to pharmacotherapy [63]. In the patient interviews, gaps in the knowledge of the patient concerning pharmacotherapy can be detected and solutions for problems can be shared with the patient. During these consultations other services can also be offered, for example synchronising all repeat prescriptions. For patients having even more problems managing medicines themselves, the pharmacist should offer to deliver medicines in week organisers.

Levels of medication review described in the UK 'Medicines Partnership' model

The Medicine partnership in the United Kingdom has defined three different levels of medication review (textbox 1)[64]. In Dutch pharmacies prescription reviews (level 1) probably routinely performed in daily practice. Treatment reviews (level 2), in which pharmacotherapy is screened by a pharmacist and feedback is given to a GP, are

increasingly popular , but not yet standard practice in many pharmacies. Dutch pharmacies also perform private pharmaceutical consultations but their frequency is still low [65]. The combined form of treatment review and medicine consultations, clinical medication reviews (level 3) is not yet regularly being performed in the Netherlands.

Textbox 1. Different levels of medication review as described in the UK 'Medicines Partnership' model.

Level 1. Prescription review	Technical review of list of patient's medicines Prescription reviews can be helpful in identifying anomalies and highlighting patients who may need clinical medication reviews. As a stand-alone tool their benefits are relatively limited as they do not normally allow for a full discussion with the patient.
Level 2. Treatment review	Review of medicines with patient's full notes Treatment reviews normally take place under the direction of a doctor, nurse or pharmacist, but often without the patient, for instance, removal of unwanted items from the repeat medicines list, and dose adjustments. This may arise from a review of patients with a particular condition such as asthma or taking a group of drugs such as proton pump inhibitors. The review may include the complete repeat prescription or focus on one therapeutic area (eg hypertension), drug (eg lithium) or group of drugs (eg NSAIDs). Recommendations may be passed to the prescriber for implementation.
Level 3. Clinical medication review	Face-to-face review of medicines and condition Clinical medication reviews require access to the patient's notes, full record of prescriptions and non drug care and results from laboratory tests etc. The review should include the complete repeat prescription as well as over-the-counter and complementary remedies. In clinical medication reviews, medicines would not be examined in isolation but considered in the context of the patient's condition and the way they live their lives. Clinical medication review should therefore involve the patient as a full partner. This means listening to the patient's views and beliefs about their medicines, reaching an honest understanding of their medicine taking behaviour, and taking full account of their preferences in any decisions about treatment. This is more than what currently happens for most patients when they visit their GP for a renewal of a repeat prescription item. The invitation to a review of an individual patient's medication (ie a type 3 review) should include both the patient and (when appropriate) the carer.

Outline of the thesis

Our research project followed the cycle of implementation. First we looked analytically at the types of problems associated with elderly and medication safety (part 1), in the second part of the thesis we tried to improve prescribing for the elderly. Textbox 2 gives an overview of the different chapters and types of research as described in the chapters mentioned.

Textbox 2. Overview of the chapters and types of research used

	Objectives	**Method**
1. Introduction	-	-
Part 1. Problems associated with elderly and use of medicines		
2. User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance	To investigate the type, number and clinical relevance of user related pharmaceutical care problems. To develop a risk model for detecting elderly drug-users at risk of user related pharmaceutical care problems	Interview study
3. Analysis of polypharmacy in older patients in primary care using a multidisciplinary expert panel	To determine the nature, volume and clinical relevance of prescription related point of attention in the elderly	Consensus method
4. Composite screening tool for medication reviews of outpatients	To examine prominent existing tools for medication review Present a new composite tool for medication review	Literature review
5. Drug induced hypoglycaemia in elderly users of anti-diabetics; incidence and risk factors	To determine the incidence rate of drug induced hypoglycaemia for the different groups of users of hypoglycaemic agents To determine risk factors for drug induced hypoglycaemia	Prospective cohort study
Part 2. Improving medication safety in the elderly		
6. Cluster controlled trial comparing two procedures for treatment reviews concerning elderly people on polypharmacy in primary care	To determine which procedure for treatment reviews (case conferences versus written feedback) results in more medication changes. To determine costs and savings related to such an intervention.	Cluster controlled trial
7. Comparison of two methods for performing treatment reviews by pharmacists and general practitioners for home-dwelling elderly people	To describe feasibility of two methods for treatment review To determine whether the process of treatment review can be improved, and by what manner.	Process evaluations by questionnaires, interviews and analysis of various features of treatment reviews
8. General discussion	-	-

Research questions

Part 1 Problems associated with elderly and use of medicines

During the preparation of our study we saw that little research has been performed on the whole range of user-related problems, we could only find studies focusing on specific types of user-related problems and studies regarding adherence to pharmacotherapy. So firstly we examined actual medication use by the elderly living in their own homes. Do elderly take their medicines as prescribed? What problems do elderly experience when taking their medicines? This was studied by means of home-interviews for 300 elderly. The results of this study are described in chapter 2.

We saw that internationally much research has been performed concerning inappropriate prescribing for the elderly living in the community. However, most of these studies have been performed with the Beers criteria, these criteria are aimed at the situation in the USA. Some of the medicines as indicated on the list are not used in the Netherlands, while other medicines used in the Netherlands considered to be inappropriate for use in the elderly are not on the list because they are not regularly used in the USA. Furthermore only one aspect of prescribing is included in most of these studies, whereas mostly different types of problems can be indicated when prescribing for the elderly is reviewed. So we performed an in-depth-analysis of the pharmacotherapy of 100 elderly drug users from our interview study. What did the GPs prescribe for the elderly, and what improvements could be made? This was studied by means of a multidisciplinary panel consisting of eight experts, individually scoring points of attention in the medication of our participants and sharing these during consensus-meetings. The results of this in-depth analysis of polypharmacy in the elderly are described in chapter 3.

Although we had a relatively high number of patients included in our in-depth analysis of polypharmacy, some types of prescribing problems, especially those that occur rarely, could have been missed or underrepresented. So we additionally searched the literature to acquire a good overview of all types of problems associated with elderly and pharmacotherapy. Out of the wealth of literature concerning prescribing for the elderly and our own studies we could identify a number of problem categories. By means of these categories we constructed a new tool for performing medications reviews in daily practice. What categories of points of attention should be kept in mind when performing treatment reviews? In this literature study different categories of problems are described, liberally provided with examples (chapter 4).

Furthermore, we saw that the majority of drug-related hospital admissions are related to a limited number of drug-classes. So, in one of our studies we looked at one of these medicine classes; hypoglycaemic agents. Some blood glucose-lowering medicines and combinations of medicines are associated with a higher risk at hypoglycaemic events, thereby increasing the risk of hospital admission. We looked for risk factors to identify users of hypoglycaemic agents at increased risk for hypoglycaemic events in a prospective cohort study in the Rotterdam-study database [66] (chapter 5).

Part 2 Improving medication safety in the elderly

For the second part of our research project we first identified which types of problems were most in need of a solution and we developed an intervention for improvement. From the studies in part 1 we concluded that there were high percentages of prescription-related

problems and the problems were of direct clinical relevance in higher proportions of patients than the user-related pharmaceutical care problems.

Although no randomised trial had been performed concerning this subject in the Netherlands, there was enough evidence from other countries that performing treatment reviews is useful. In our study we investigated the best method for performing treatment reviews in daily practice. From the scientific literature it is known that personal feedback (case-conferences) is more effective than written feedback when influencing prescribing behaviour. In our study we wanted to determine whether this is also the case for treatment reviews and whether extra costs caused by extra time expenses can be covered by supplemental savings on medication costs. We studied this by means of a cluster controlled trial. The results of this intervention-study are described in chapter 6.

To study feasibility in day-to-day primary care and to study whether improvements in the process could be made we also performed a process evaluation. We used written questionnaires, structured interviews and process parameters as gathered during the intervention study. The results of this process evaluation are described in chapter 7.

Chapter 8 concludes the thesis with a general discussion, the results of the different studies are discussed and recommendations for further research and for improving the performance of treatment reviews in daily practice are given.

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Chapter 2

User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance

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Abstract

Background and objectives: Many studies determined the number and nature of user-related Pharmaceutical Care Problems (PCP) and factors affecting them, but none considered the inclusion of clinical relevance.The aims of this study are (i) to investigate the type, number and clinical relevance of user-related PCP self-reported by home dwelling elderly on polypharmacy and (ii) to develop a risk-model for detecting elderly drug-users at risk of user-related PCP.

Methods: The study was a cross-sectional study conducted among 286 home dwelling elderly on polypharmacy (≥ 75 years, ≥ 4 medicines) in the Netherlands. The user-related PCP found were divided into problem categories and subsequently a pharmacist and a general practitioner classified the problems into those with low and those with (potential) clinical relevance. Factors possibly associated with PCP (both for all and relevant problems) were identified, and subsequently tested in multivariate models using logistic regression.

Results: Three hundred and ninety-eight user-related PCP were observed in 189 patients (66% of all participants). After classification of user-related PCP only 26% appeared to be of potential clinical relevance (26% of all participants). When including clinical relevance a shift in predominantly present problem categories is observed. Furthermore, the risk model for problems with potential clinical relevance contains more factors than the model which considered all problems. Factors associated with clinically relevant PCP are emotional or physical problems interfering with social life, communication skills (vision and hearing), using tablets that have to be divided, using inhaled medicines, and the number of medicines used. This risk-model has a specificity of 92% and a sensitivity of 32%.

Conclusions: Although user-related PCP were seen in about two-thirds of the participants, in only one out of four participants was the PCP considered to be of potential clinical relevance. With inclusion of clinical relevance, other problem categories become more dominant. A specific risk model is designed to select elderly patients that are most likely to have PCP in need of more urgent intervention. Unfortunately higher specificity is accompanied by low sensitivity in the present model.

Introduction

Pharmacists aspire to reduce drug-related problems by monitoring and advising elderly patients as well as their physicians[1]. To further this ambition, our study analysed user-related and prescription-related pharmaceutical care problems (PCP) and their determinants in home-dwelling drug-users who were at least 75 years old and who were taking at least four medications chronically. The study concerning user-related problems is described here, whereas details of the prescription-related problems will be reported elsewhere.

Unlike previous studies, we not only evaluate the nature and prevalence of user-related problems, but also estimated their potential clinical relevance. In other words we assessed whether the solving of these user-related problems could actually lead to an improvement in the health status of the particular patient. Furthermore, we measured various characteristics of users that have been described as potential determinants of user-related problems. Besides social and demographic characteristics (e.g. age, socio-economic status, educational level, living conditions), we recorded the number and nature of prescription medicines, the use of non-prescription medicines, the number and medical specialisation of the physicians seen, and the frequency of doctor visits[2–7]. We also assessed cognitive function and emotional wellbeing, because impairments in these domains have been repeatedly associated with non-adherence[2,3,8–12]. We hoped that the evaluation of these factors would allow us to develop a reliable risk model that would help community pharmacists to detect elderly drug-users at increased risk of clinically relevant user-related problems. These would more likely require urgent pharmaceutical care services.

Methods

Study design

The study was a cross-sectional study conducted among 286 home dwelling elderly in the Southern part of the Netherlands, with data collected from November 2001 to February 2003.

Study population

The participants were selected from the pharmacy records of a convenience sample of nine pharmacies in the Southern part of the Netherlands. The pharmacies were located in villages, small towns and medium-sized cities. Eligible patients were those who were (i) 75 years or over, (ii) living at home and (iii) taking four or more medications on a regular basis. Elderly patients who were terminally ill, lived in a nursing home or in a home for the elderly were excluded from the study. Signed consent was obtained from participants before the onset of data-collection. Non-responders were reminded by telephone after

several weeks. Patients who refused participation were asked for their reasons, age and the number of medications they were currently taking.

Variables and instruments

USER-RELATED PHARMACEUTICAL CARE PROBLEMS

User-related PCP were defined as:

1. *Non-adherence to prescribed treatment* (e.g. underuse, overuse, deviation from the dosage schedule), which has been reported to occur in 14–56% of the patients, depending on the definition of non-adherence and on study populations[2, 3, 5, 13–16].

2. *Problems with correct self-administration of medications*, such as difficulties with dividing tablets[17,18], opening packages[3,19,20], or using eye drops[21,22], inhalation devices or other special dosage forms. In one study, 41% of elderly inpatients were unable to perform one or more tasks that were needed when using their medications, such as opening containers or strips and dividing tablets[23]. In other studies, 41–44% of all elderly patients using inhalation medicines had problems with the correct use of these devices[24–26].

3. *Inappropriate medicine-taking habits*, such as taking medicines that are out of date, or lending prescribed medicines to others. These habits have been reported in 6 and 7% of participants respectively[20].

CLINICAL RELEVANCE OF USER-RELATED PHARMACEUTICAL CARE PROBLEMS

A pharmacist and a general practitioner classified problems into PCP with low clinical relevance and PCP with potential or high clinical relevance; this was based on the most likely reason for use.

Problems were considered as having clinical relevance, if they had a potential harmful effect on the general health status of the patient. Each problem was discussed until the physician and pharmacist reached consensus.

FACTORS POSSIBLY ASSOCIATED WITH USER-RELATED PHARMACEUTICAL CARE PROBLEMS

- Socio-demographic characteristics: age, sex, marital state, income, living situation, general practitioner and dispensing pharmacy.
- General health measured by the COOP/
- WONCA charts on physical fitness, feelings, daily activities, social activities, change in health and overall health[27]. For analysis, the five point-scales were dichotomized, by grouping the positive and negative answers.
- Impairment of activities of daily living was measured by the Groningen Activity Restriction Scale (GARS, ADL-scale)[28]. The total score on the GARS-ADL was used in analysis.

- Mental health measured by the Hospital Anxiety and Depression Scale (HADS)[29,30]. The total score and the total scores on the anxiety and the depression sub-scales were used for analysis.
- Cognitive impairment, measured by the Mini Mental State Examination[31]. The maximum total score of the original instrument is 30. As our questionnaire lacked one question in the area of orientation, participants could score a maximum of 29.
- We also probed whether the participant knew the indications for all medicines as a measure for cognition.
- Medical consumption: number of medicines taken, number of prescribing physicians, hospital admission in the last 3 months, number of physician and pharmacy visits in the last 3 months.
- Receiving help with managing medication.
- Drug administering characteristics: having problems with reading and understanding instructions on medicine-labels, having problems with opening packages, strips or with using administration aids, having problems with subdividing tablets or with using adherence aids.
- Medicine-taking characteristics: using prescription and OTC medicines which were classified according to the Anatomical Therapeutic Chemical Classification of the WHO Collaborating Centre for Drug Statistic Methodology[32].
- Communication problems: having difficulties in conversing with one other person or a group of three people, having problems with reading newspapers or in recognizing people.

Data collection

Data were collected from the registration records at the pharmacies, by self-administered questionnaires, and by face-to-face interviews with participants.

Data on prescribed medications of participants were obtained from the registration records of the nine participating pharmacies. The researcher (pharmacist) used these data to point out potential user-related PCP that needed to be probed on during the interview.

Subsequently, participants received self-administered questionnaires to be completed before the face-to-face interview took place. The questionnaires included questions on patient characteristics that were believed to be determinants, such as age, sex, education, income, and the scales that measured depression, anxiety, general health and functional validity. The face-to-face interview was used to probe actual use and administration of medicines and to probe on topics not covered by the written questionnaire, such as cognition, OTC drug use, use of adherence aids and drug administration devices. During

the interview, participants were asked to present all medications they were regularly taking and to indicate for each medicine the purpose of the medicine, the dosage schedule and skipped doses. If the reported dosage schedule differed from the schedule recorded at the pharmacy, the participant was asked for the reason.
The interviews took place at the participant's homes and were conducted by trained interviewers with a background in health sciences (medical students), pharmacy (pharmacy assistants) or general practice (practice assistants).

Data analysis
Interview data were entered in a MS-ACCESS database and analysed using SPSS 11 (SPSS Inc, Chicago, IL, USA).
User-related PCP were counted and classified into those with low clinical relevance and those with potential clinical relevance by a pharmacist and a general practitioner.
Potential determinants were analysed by making comparisons between:

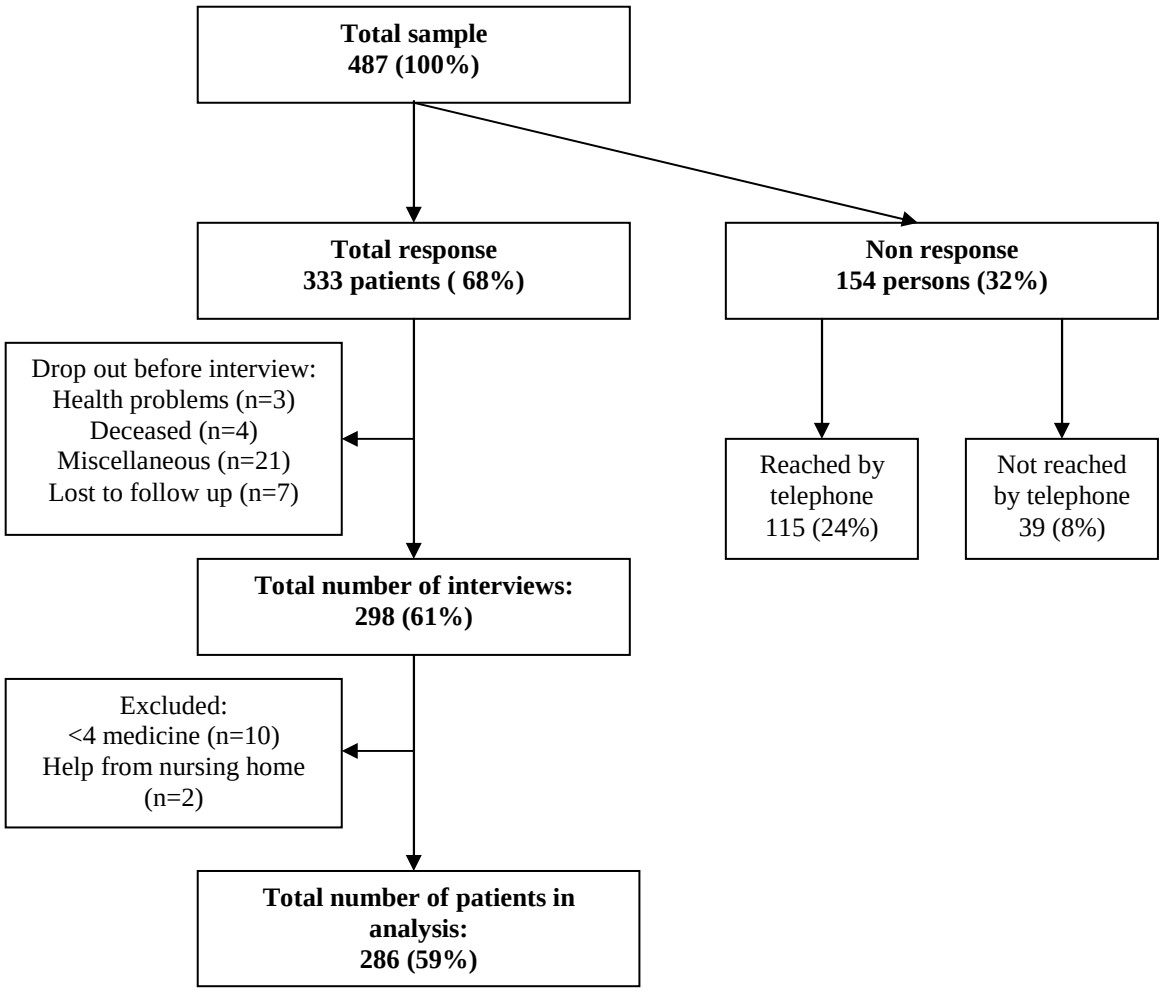
- Participants having at least one user-related PCP and participants having no PCP at all.
- Participants having at least one (potentially) clinically relevant PCP and participants having only non-relevant or no PCP at all.

Comparisons were made on factors that are possibly associated with PCP. The significance of bivariate associations was determined by t-tests (for numeric values), a chi-square-test (for count data), and Mann–Whitney U-tests when data had been measured at the ordinal level. Factors that were significantly associated at the bivariate level, were tested in multivariate models using logistic regression. The dependent variables in logistic regressions were (i) having at least one user-related problem or (ii) having at least one user-related problem of (potential) clinical relevance. As the HADS and its subscales for depression and anxiety were highly correlated, only the subscales were tested at the multivariate level.

Results

Participants
A flowchart of the response of the patients is presented in Fig. 1, showing that out of the 487 eligible patients, 333 agreed to participate. Of these 333 participants, 35 dropped out, resulting in a total of 298 interviews. During analysis, another 12 patients had to be excluded because they did not meet the inclusion criteria. All analyses were conducted on the remaining 286 patients (net response 59%).

Figure 1: Flowchart of response of participants



The characteristics of the 286 participants are described in Table 1.

A non-response analysis comparing participants with non-responders by age and number of medicines taken showed that responders used more medicines ($P < 0.01$); on average 6.6 as compared with 6.0 by non-participants.

Table 1. Characteristics of participants (n=286)

	Participants (n=286)
Age, mean (SD)	80.3 (3.7)
Mean no. of prescribed medicine (SD)	6.6 (2.2)
Sex (% of participants being male)	36
Living situation (% of participants living alone)	53
Level of education (% of participants with only primary education)	30
Hospitalisation (% of participants which was hospitalised last 3 months)	4
Prescriptions (% of participants which gets prescriptions only by one physician)	46
Adherence aids (% of participants using a medicine box)	24
Help with medication (% of participants which gets help with managing medication)	55

Number of user-related pharmaceutical care problems and their clinical relevance

A total of 398 user-related PCP were observed in 189 patients, implying that 66% of all participants reported at least one user-related problem and that participants usually had more than one user-related problem. Table 2 shows the distribution of PCP's over the different types of problems. The most common user-related PCP, seen in 45% of patients, was using less medication than prescribed. This was followed by problems with breaking tablets (seen in 16% of all participants and 36% of all participants who had to divide tablets) and discrepancies in dosing schedule, seen in 11% of all participants.

Table 2. Distribution (in percentages) of PCP over the various problem categories categorised by seriousness of user related PCP

Nature of problem	All PCP (n=398)	PCP with minimal clinical relevance (n=295)	PCP with potential clinical relevance (n=103)	Example of PCP with minimal clinical relevance	Example of PCP with potential clinical relevance
Using less than prescribed	53	62	27	Hypnotic not used daily	Hydralazine used 2 times daily instead of 3 times daily
Problems with dividing tablets	11	13	6	Problem with dividing tablets of antihypertensives	Problem with dividing amiodarone tablets
Deviation in dosage schedule (total daily dose is as prescribed)	9	9	8	Tolbutamide taken as 2 tablets in the morning and 1 in the evening instead of 1 tablet 3 times daily	Simvastatin taken am instead of pm
Problems with using eye drops	9	4	22	Problem with eye drops without pharmacologically active ingredient	Problem with ocular beta-sympathicolytics for use in glaucoma
Using more than prescribed	6	4	12	Lactulose syrup taken twice daily instead of once daily	Additional tablet of zopiclone taken during night when waking up (almost every night)
Use of former prescribed medicine	3	3	3	Temazepam	Mefenoxalon
Lends medicine to another person	3	3	2	Paracetamol	Diazepam
Prescription medicine discontinued on patient's own initiative	2	1	5	Discontinuation of acetylcysteine	Discontinuation of theophylline
Has problems by using inhalation medicine	2	-	6	-	Flixotide
Miscellaneous	4	2	10	Patient tries sometimes if lactulose can be stopped for a while	Patient forgets often to take the patch with transdermal nitro-glycerine off at evening.

PCP= pharmaceutical care problems

After classification of user-related PCP into problems with minimal/no clinical relevance and problems with potential clinical relevance, it appeared that only 26% of all PCP could be considered as having a potential clinical relevance. Similar figures are seen at the level of the participants, with 58% of the total number of participants only having user-related PCP that were likely of no or minimal clinical relevance, 73 participants (26%) showed at least one PCP with potential clinical relevance.

Furthermore, when clinical relevance was included, other problem categories became more prominent. Using less than prescribed amounts of medication is also in the category of clinical relevant problems the problem seen most (seen in 9% of all participants). This is followed by having problems using eye drops (seen in 5% of all participants) and using more than prescribed amounts (seen in 4% of all participants) (Table 2).

Risk model for user-related pharmaceutical care problems

A comparison of participants with user-related problems to participants without problems, showed that, at the bivariate level, significant factors ($P < 0.05$) were using a higher number of medicines, using tablets that had to be divided, using at least one medicine out of the ATC-groups A or N and having problems with reading and understanding the instructions on the labels. At the multivariate level, three factors remained significant: a higher number of medicines, using tablets that had to be divided, and problems with understanding the instructions on the labels (Table 3).

Table 3. Logistic regression model for PCP and for PCP with potential clinical relevance

	All PCP			PCP with potential clinical relevance		
	B	**Exp (B)**	**95% CI**	**B**	**Exp (B)**	**95% CI**
Number of medicines taken (for each suppl. medicine)	0.306	1.358**	1.172-1.573	0.177	1.194*	1.036-1.377
Participant has to divide tablets	0.584	1.793*	1.038-3.095	0.959	2.609**	1.373-4.960
Participant has problems understanding instructions on the medicine label	1.223	3.397	0.959-12.033	-	-	-
Interference of emotional or physical problems with social life	-	-	-	0.798	2.221*	1.061-4.648
Participant has problems with talking to another person	-	-	-	0.883	2.417*	1.121-5.214
Participant has problems in recognising people	-	-	-	0.734	2.083*	1.058-4.103
Participant uses inhalation medicines	-	-	-	1.425	4.159**	2.048-8.446

* $p<0.05$
** $p<0.01$
PCP= pharmaceutical care problems

Comparing participants with at least one potentially clinically relevant problem to participants with only problems of low clinical relevance or no problems at all showed significant bivariate associations ($P < 0.05$) with a higher number of medicines taken,

using tablets that have to be divided, worse general health of participants, and participants having problems with hearing and vision. In addition, mental health (feeling anxious or depressed, experiencing emotional problems and feeling that emotional or physical problems interfered with social life) and the usage of special dosage forms (inhalation devices and eye drops) increased the likelihood of having problems that were potentially of clinical relevance. As Table 3 indicates, six factors remained significant at the multivariate level: using a higher number of medicines, using tablets that have to be divided, interference of emotional or physical problems with social life, problems with talking to another person, problems in recognizing people and using inhalation medicines.

The predictive values of both models showed that the model for having PCP (relevant and nonrelevant) had a reasonable sensitivity, as it could select 85% of all participants who are at risk for having user-related PCP, although the specificity (excluding those who are not at risk) was only 26%.

The specificity of the second model was high (93%), but the sensitivity was still low at 32%.

Discussion

User-related PCP were reported by two-thirds of home-dwelling drug users, who were at least 75 years old and who were taking at least four medications chronically. The most common types of problems were underuse, difficulties with dividing tablets, deviations from the prescribed dosage schedule without changing the total daily dose, problems with the application of eye drops and overuse. Use of formerly prescribed medicines, lending medicines to others, or discontinuation of prescribed medicines without consulting the prescriber were only sporadically recorded. Our data on under-use and over-use (observed in 53% of all participants, if taken together, with patients often being non-adherent to more than one medicine) correspond fairly well with the findings of others, who observed that 14–56% of their patients did not comply for at least one prescribed medicine[2,3,5,13–16]. The difficulties identified, concerning the dividing of tablets, the use of eye drops or inhaling medicines have also been described previously[17–19,22–26]. McElnay et al.[16] found that inhaled bronchodilator medicines are related to non-adherence and that patients are likely to adapt the required doses of inhaled medicines to their physical condition, which is consistent with the findings of our study. The strong association between using inhaled medicines and user-related PCP is probably mainly due to non-adherence and to a lesser extent to self-reported administration problems.

Unlike previous studies, we assessed the potential clinical relevance of the reported problems. This revealed that the majority of user-related PCP was unlikely to cause clinically significant problems and that other types of problems became more prominent.

For instance, 14% of the cases concerning under-use involved the reduced intake of benzodiazepines compared to the prescription, which is certainly not a change for the worse. Only one-fourth of all PCP could be considered as being of potential clinical relevance (Table 2). This implies that studies which do not take the degree of clinical relevance into consideration focus too much on problems that do not really matter.

Paying attention to problems of potential clinical relevance is also important in the development of a predictive risk model for helping community pharmacists to identify elderly drug users at increased risk of user-related PCP. When clinical relevance was not taken into account, only the (higher) number of medicines taken, the ability to understand the instructions on the labels and having to divide tablets emerged as principal risk factors. When potential clinical relevance was considered, however, other risk factors besides the number of medicines taken and having to divide tablets became prominent, namely using inhalation-medicines, the capability to recognize people, to have a conversation, and the extent to which patients felt that emotional problems and physical disabilities limited their social functioning. Although others have sometimes reported these determinants[2–4,6–11,13,15,33–35] this is the first time that their importance for the occurrence of clinically relevant problems has been demonstrated.

Our study is not without limitations. First, we relied on self-reports of problems, which may lead to an underestimation, e.g. of non-adherence problems. Our interviewers occasionally observed that participants could not provide a satisfactory explanation, when the interviewers confronted them with an interruption in the dispensing pattern of their chronic medicines (as established by consulting their pharmacy records). They still stated that they had taken the medicine as prescribed. This problem may also arise in daily pharmacy practice, and is just as difficult to solve as in our research setting. A second limitation is that nonresponders differed from responders by using fewer medicines, which may have led to a slight overestimation of the PCP per patient. Furthermore, the pharmacists and general practitioners who took part in the study were a convenience sample and we do not know to what extent a selection bias may have occurred. This selection bias may also be seen in the response of the invited participants. Participants familiar with noncompliance are likely to be less inclined to take part in a study concerning drug-taking habits. Finally, our study did not comprise highly urbanized areas. This may have led to an under representation of immigrant drug users, who might have different types of PCP compared with our study population.

The risk model we developed to predict the detection of PCP with potential clinical relevance had a high specificity (93%) but unfortunately a low sensitivity (32%). This has also been found by another research group, who developed a risk model for non-adherence in elderly patients prior to hospitalization[16]. The practical implication is that the

determinants found with our model can support community pharmacists in achieving early successes. They can start with intensifying their care for elderly patients, by asking three simple questions on health and the communication ability of the user, supplemented with information on the total number of medicines used and dosage form of each medication. This information can also be easily extracted from the pharmacy dispensing record. The model is not suitable, however, for the identification of all elderly patients who are at higher risk and have an increased need of pharmaceutical care services. For that purpose, further research will be necessary with our model providing a potentially useful starting point.

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Chapter 3

Analysis of polypharmacy in older patients in primary care using a multidisciplinary expert panel

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Abstract

Background: Many older patients suffer from chronic diseases for which medicines should be used. Because of the higher number of medicines used and decline in hepatic and renal function, older patients are more prone to problems caused by these medicines.

Therefore, it is important to review pharmacotherapy concerning older patients in primary care in a reliable way.

Aim: To determine the nature, volume and clinical relevance of prescription-related points of attention in the elderly.

Design of study: Analysis of pharmacotherapy by a multidisciplinary expert panel consisting of GPs, geriatric specialists, clinical pharmacists and community pharmacists.

Setting: Pharmacotherapy of 102 home-dwelling older patients on polypharmacy (≥75 years, using ≥4 medicines continually) living in the Netherlands.

Method: The analysis of medication-profiles was based on a two-round consensus method.

Results: When performing medication reviews for older people it seemed that for almost all (98%) improvement in pharmacotherapy could be made. For 94% of all patients points of attention could be identified in prescribed medicines, of which 30% was considered to be of direct clinical relevance. In 61% of all patients a medicine could be added to improve pharmacotherapy, 25% of these prescribing omissions were considered to be of direct clinical relevance.

Conclusion: The regular performance of medication reviews should be part of routine in primary care as it yields significant numbers of prescription-related points of attention. Although they were not all considered to be of direct clinical relevance, all points of attention do ask for a signal to the prescribing physician. This paper is not implying poor practice or poor reviewing practice but documenting the need for performing regular medication reviews.

Introduction

In the Netherlands 14% of the population consists of older people (≥ 65 years old). This proportion of the population is responsible for as much as 39% of all expenses on medicines as delivered by community pharmacies. People aged 65 years or over use three times as many medicines as compared to the whole population in the Netherlands (three medicines daily on average). People of 75 years or over use on average as many as four medicines daily.[1] Older people use many medicines because they suffer from more chronic conditions that need treatment by means of pharmacotherapy. However, older people are more prone to adverse drug reactions, resulting from age-related factors such as changes in drug distribution, metabolism and excretion, and in receptor sensitivity as well as from drug–drug interactions and drug–disease interactions caused by prescribing of multiple drugs.[2–5] In other words, prescribing in older patients involves balancing conflicting demands, and the benefit:risk ratio should be considered when deciding whether to initiate pharmacotherapy.

Although it is not possible to prevent all prescription-related problems in older people, several studies have shown that it is possible to reduce the occurrence of prescription-related problems by means of a medication review.[6–9] In such a medication review, complete pharmacotherapy of an individual patient is assessed by a trained professional (GP and/or pharmacist). In the UK regular medication reviews for older people on long-term medication were recommended by the Department of Health to maximise therapeutic benefit and minimise potential harm,[10] and this practice has been included in the Community Pharmacy Contractual Framework for all patients on long-term medication in the UK.[11]

In this article we describe the occurrence and clinical relevance of prescription-related points of attention found in older patients when use is made of an in depth and comprehensive approach with medication reviews performed by both prescribers and pharmacists. The occurrence of user-related pharmaceutical care problems in the same group of older patients had been determined in a previous study,[12] creating insight in to whether it appears more effective to focus quality improvement interventions on prescribers (in particular GPs), or on the users of medicines.

This study is the first in-depth analysis by a large expert panel and focuses on a wider and more comprehensive set of prescription-related points of attention than previous studies have done.[13–21] It therefore provides a more complete and accurate picture of the size and types of prescription-related points of attention faced by older patients as well as the clinical relevance of them. Whether or not precautions were taken by the prescribing physician (such as regularly checking potassium levels) to prevent these potential problems is not included in this study. However, the results of this study should give some insight in

to the process of medication review that can be used for setting up better and more reliable medication reviews in the future.

Method

Study design and population

An analysis was performed of pharmacotherapy of 107 older people living in the community in the southeast of the Netherlands. Pharmacy dispensing data were collected from November 2001 to December 2002. The assessment of pharmacotherapy by the expert panel was based on a consensus method.

Patients were selected from the participants of a study on user-related problems[12] with 298 homedwelling participants of ≥ 75 years old who were being prescribed four or more medicines chronically, and were living in the south of the Netherlands. In the previous study, nine pharmacies were included (convenience sample). These pharmacies each contacted one to three GPs. The pharmacists and GPs invited eligible patients to participate in the study: patients were included if they returned the application form, including their informed consent. For each GP participating in this study (n = 18), six patients were picked at random, resulting in a total of 107 patients (for one GP only five eligible patients could be pointed obtained).

Variables and instruments

Types of prescription-related points of attention. Inappropriate prescribing was assessed based on the aspects described in Table 1.

Table 1. Aspects of inappropriate prescribing including examples for each aspect

	Example	Description of the problem
1.	Medicine not useful (no indication, no proven effectiveness or better/safer alternatives available)	Prescribing clofibrate, for which much safer and more effective alternatives exist
2.	Medicine inappropriate for use in older patients	Prescribing diazepam, which has a long half-life time
3.	Prolonged prescribing of hypnotics	Medicine is not taken for a correct duration
4.	Dosage exceeds the suitable dosage for older patients	Prescribing flurazepam in a dosage exceeding 15 mg daily
5.	Unnecessary therapeutic duplication	Prescribing cylcobarbital and a benzodiazepine
6.	Contraindication known (drug-disease interaction)	Prescribing indometacin to a patient suffering from heart failure
7.	Medicine used for treatment of a side-effect caused by another medicine	Omeprazole for treatment of stomach problems probably caused by ketoprofen (NSAID)
8.	Interaction with another medicine (drug-drug interaction).	Prescribing cotrimoxazol to a patient using acenocoumarol (coumarin-derivative) that causes problems in managing INR
9.	Omission of drug therapy that is indicated for the treatment or prevention of a condition	Lack of prescribing a laxative to a patient
10.	Medicine used in/provided by unsuitable administration aids for older people	Prescribing different types of inhalation devices to one patient

Clinical relevance of prescription-related points of attention. Panel members rated the clinical relevance of points of attention and prescribing omissions by means of a score from zero to three. Points of attention were considered as having clinical relevance if they could lead to a deterioration in general health status of the patient (see Table 2).

Table 2. Levels of clinical relevance for prescription related pharmaceutical care problems, including examples for each score of clinical relevance

Score	Description	Example
0	Aspect is not applicable	-
1	Aspect is applicable, but not clinically relevant	Use of vitamin C preparations without an indication known
2	Aspect is applicable and potentially clinically relevant; extra information is needed to determine the relevancy of these points of attention (such as blood pressure, other measurements or clinical condition of the patient)	Drug-drug interaction between digoxin and diuretics, when potassium levels are regularly checked this interaction will not cause any problems.
3	Aspect is applicable and clinically relevant; these aspects are of clinical relevance in all instances	Prescribing glibenclamid, which is not suitable for use in older patients because it can cause prolonged hypoglycaemia

Procedures

Expert panel. The expert panel consisted of two GPs, two community pharmacists, two olderpatient specialised internal medical specialists and two clinical pharmacists. Panel members were selected on the basis of their nationally recognised expertise in pharmacology and/or clinical older patient pharmacology.

Individual scoring. For each of the 107 participating older patients the panel members received a pharmacy record, a graphic medication record, the reasons for prescribing the medicines (provided by the GP), and a scoring form, containing all medicines regularly taken as determined by pharmacy records and the previously named aspects (see Table 1).[10] The scoring forms were completed and sent back to the researcher by individual panel members. Before the consensus meetings, panel members received overviews in which their own scores were reflected in the light of the scores of the other panel members.

Consensus meeting. During the consensus meetings aspects of medicines were discussed that indicated a lack of consensus or were of clinical relevance. The researcher (a pharmacist) selected the points of attention that needed further discussion, including all items that had a score of at least six (when taking scores of all experts together) and all items that had scored at least a single three (clinically relevant item). An independent chairperson led the meeting. Panel members were invited to raise any additional topic that they considered of concern.

In case panel members were not able to join the meeting the researcher held an individual interview with the panel members to discuss his/her scores, and brought it into the discussion during the group meetings.
After the panel meeting, reports of the meeting, made by the researcher, were sent by email to all panel members, so that they could give their comments. Issues that remained unclear and comments of panel members were discussed again during the next consensus meeting, until consensus was reached.

Data analysis. After the panel discussions the scored points of attention (consensus) were analysed with SPSS 11 (SPSS Inc. Chicago, Illinois, US), and an inventory of all prescription-related points of attention was made. During the panel discussions it seemed that a score of 1 was not always used consequently; when an aspect was not relevant it was not scored at all. Therefore, in the results, only points of attention with a score of 2 (potential clinical relevant) or 3 (clinically relevant) are included.

Results

Consensus meetings

In total, five panel discussions (four on telephone and one in person) took place during which the medications of 107 patients were discussed. On average, there were more than six panel members present during the panel discussions (one time, all experts were present, one time only five experts were able to participate, for two discussions six panel members participated and in one instance seven panel members were present).
On average, the total panel consensus contained more (and other) points of attention than the individual scoring lists. It appeared that each panel member had his/her own area of expertise. The individual written score κ value showed a variation for each item and each panel member (range 0.01–0.88). The average κ value after the round in writing for all items and all panel members was 0.34 (slight agreement). The discussion sometimes yielded additional points of attention because of the interaction between panel members of different professions. During the consensus meetings, however, consensus was reached for all items.

Patients

In the panel discussion the medications of 107 elderly patients were discussed. After an evaluation of medicine use, five older patients were excluded because they used fewer than four medicines. The included patients were on average 81 years of age, were almost two-thirds female (62%), and used on average 6.8 medicines chronically. Forty-one per cent of the included patients got their prescriptions only from one physician.

In total, 102 older patients used 755 medicines. Medicines for cardiovascular diseases were prescribed most frequently (36% of the total number of medicines used), followed by medicines for the central nervous system (13%), the alimentary tract and metabolism (12%), and blood and blood-forming organs (10%).

In the medication records of 98% of all patients, points of attention were identified. In 4% of these medication profiles the expert panel had no comments on the medicines currently used, but one or more medicines could possibly or should be added to improve pharmacotherapy.

Number, type and clinical relevance of prescription-related points of attention

Panel members rated 457 points of attention considering prescribed medicines used by 96 older patients. Thirty per cent of these recommendations were considered to be of direct clinical relevance, the remaining 70% was considered to be of potential clinical relevance. The latter category of problems can possibly partly be solved by reviewing the medical records (such as measures of potassium or blood pressure), but whether or not these measures were regularly performed by the GP was not registered in our study.

Table 3 shows the distribution of the points of attention by various problem categories.

Medicines considered as being not useful are reported most frequently, seen in anatomical therapeutic classification (ATC) group N (medicines for the nervous system, 21%) and C (medicines for the cardiovascular system, 20%). The problem category seen second most frequently is prescribing medicines for an incorrect period of time, almost exclusively (88%) seen in ATC group N, and prescribing medicines in a dose not appropriate for older people, seen in group C (56%) and N (40%). Drug–drug interactions are also reported frequently, drug–drug interactions are mainly (57%) caused by medicines from ATC group C, medicines for the cardiovascular system.

Table 3 Number and types of prescription-related points of attention (including points of attention with potential clinical relevance and points of attention with direct clinical relevance)

Type of prescription related point of attention	Number of prescription-related points of attention (% of total number of prescription-related points of attention)
Medicine not useful (no indication, no proven effectiveness or better alternatives available)	76 (19)
Dose not appropriate for > 75 years	57 (14)
Incorrect period	57 (14)
Medicine interaction	55 (13)
Medicine inappropriate for > 75 years	51 (13)
Inappropriate administration form or aids	48 (12)
Medicine used for treatment of side effects of another medicine	27 (7)
Contraindication known	19 (5)
Unnecessary therapeutic duplication	18 (4)
Total	**408 (100)**

Table 4 shows the percentages of medicines out of main ATC groups having at least one prescription-related point of attention of potential clinical relevance. The main ATC group R (medicines for the respiratory system) is the group with the highest number (relatively); this is mainly caused by concerns of panel members about the suitability of the inhalation devices for elderly patients, but also about the use of mucolytics. There is some doubt whether these preparations are effective. At the time of our study, the leading Dutch Drug Compendium (Farmacotherapeutisch Kompas) discouraged the use of oral mucolytics, this discouragement is still present in the 2006 edition.[22] The panel felt that their use should, at the very least, be carefully considered.

Table 4. Number of recipes within a main anatomical therapeutic classification (ATC)-group[a]

Main ATC-Group	Number of recipes with at least one prescription-related point of attention (% in main ATC-group)	Total number of recipes in main ATC-group	Type of prescription related point of attention seen most within the particular main ATC-group (percentage in main ATC-group)
A. Alimentary tract and metabolism	30 (32.3)	93	Medicine for treatment side-effect of other medicine (20.5) Medicine not useful (8.7)
B. Blood and blood forming organs	19 (24.4)	78	Medicine not useful (15.4) Drug-drug interaction (8.9)
C. Cardiovascular system	97 (35.7)	272	Drug-drug interaction (18.0) Dose not correct for > 75 years (11.8)
G. Genitourinary system and sex hormones	8 (66.7)	12	Medicine not useful (41.6) Medicine not suitable for > 75 years (33.3)
H. Systemical hormonal preparations (excl. sex hormones and insulin)	6 (31.6)	19	Unnecessary therapeutic duplication (15.8) Medicine not useful (10.6)
J. Anti-infectives for systemic use	3 (42.9)	7	Length of prescription (28.6) Drug-drug interaction (14.3)
M. Musculoskeletal system	28 (73.7)	38	Drug-drug interaction (26.4) Medicine not suitable for > 75 years (26.3)
N. Central nervous system	65 (65.0)	100	Length of prescription (50.0) Medicine not suitable for > 75 years (27.0)
R. Respiratory system	58 (90.6)	64	Administration form not suitable for > 75 years (73.4) Medicine not useful (20.4)
S. Sensory organs	4 (9.5)	42	Medicine for treatment side-effect of other medicine (4.8) Length of prescription (4.8)

[a] with at least one point of attention (including points of attention with potential clinical relevance and points of attention with direct clinical relevance), total number of recipes in main ATC-group and a description of the type of points of attention seen most (percentage of all points of attention in the main ATC-group)

Main ATC group M (medicines for the musculoskeletal system) is the group with the second highest number of points of attention, mainly caused by drug–drug interactions caused by NSAIDs (26%), use of hydroquinine or NSAIDs being less appropriate for the elderly (26%), and use of NSAIDs when other analgesics are indicated (18%).

In the main ATC group G (medicines for the genitourinary system and sex hormones) recommendations were related to medicines for incontinence with a marginally proven effectiveness (while leading to side effects) for which alternatives exist causing fewer side effects (42%) and inappropriateness for older people because of anticholinergic side-effects (33%). In group N (medicines for the nervous system) points of attention were mainly related to prolonged prescribing of benzodiazepines (50%). Points of attention in this group were aimed at prescribing long-acting benzodiazepines that are less suitable for use in the elderly (27%) and prescribing drugs —mainly benzodiazepines— in dosages exceeding the geriatric daily dose (23%).

In some ATC groups, high percentages of prescriptions have at least one recommendation. These recommendations can be categorised into specific groups of points of attention, more than half of all points of attention can be identified by looking at these specific medicines or groups of medicines.

Prescribing omissions

By reviewing the complete medication profiles, it appeared that 101 medicines might have been needed to improve the quality of medication therapy in 62 patients (61% of all older patients). Score 2 (a medicine might be added to improve pharmacotherapy depending on the general condition of the patient) was scored in 76% of all cases and seen in 52% of all older patients. Twentyfive per cent of the omitted medicines had a score of 3, meaning that according to prescription guidelines a medicine should be added to improve pharmacotherapy. These prescribing omissions were seen in 23% of all elderly patients.

More than half of all prescribing omissions (60%) were found in main ATC group C (medicines for the cardiovascular system), for example, the need of adding an ACE-inhibitor to pharmacotherapy of an elderly patient with heart failure. Twenty-two per cent of the prescribing omissions could be categorised in main ATC group B (blood and blood forming organs), such as adding a thrombocyteaggregation- inhibitor to the pharmacotherapy of an older patient with angina pectoris. Ten per cent of all omitted medicines belonged to main ATC group R (respiratory system); a medicine should probably be added to optimise ATSMA/COPD treatment, such as rescue-medication (short-acting β_2-sympathicomemetica) for the treatment of a patient only using long-acting β_2-sympathicomimetica.

Discussion

Summary of main findings

In this study, prescription-related points of attention of potential clinical relevance were found in pharmacotherapy of almost all included patients. One-third of the points of

attention found in prescribed medicines were considered to be of direct clinical relevance, implying that these prescriptions should be changed unconditionally. The remaining two-thirds were potentially relevant, meaning that adjustment would depend on clinical measurements or specific clinical parameters of the patient, whether or not these precautions were taken by the physician was not registered in our study. In addition, the panel determined that a relevant medication was missing or potentially missing in almost two-thirds of the patients.

Strengths and the limitations of the study

This study is the first in-depth analysis by a large expert panel and focuses on a wide and comprehensive set of prescription-related points of attention. It provides a complete and accurate picture of the number and types of prescriptionrelated points of attention faced by older patients as well as the clinical relevance of these problems.

Our study is not without limitations. First, the patients in our study consisted of a limited sample. Although their number was quite high for such a comprehensive method of evaluation, some types of prescribing problems — in particular those that occur rarely — may be underrepresented. Second, consensus approaches always entail a risk that some panel members are more influential than others. Third, our expert panel has identified points of attention on the basis of a medication record and the indications for the medicines as given by the physician. Our panel had no medical records at their disposal. In most instances, regular checks and measurements will be performed by the physician and in some instances a second choice medicine will be optimal treatment because other medicines will not be tolerated by the particular patient. Our study does indicate a high number of points of attention in daily practice. However, a part of these points of attention will be dealt with already by means of regular checks. This paper is not implying poor practice or poor reviewing practice but documenting the need for regular medication reviews.

Comparison with existing literature

Recommendations were mainly seen in the medicines for the respiratory system, the cardiovascular system and the nervous system. Points of attention regarding medicines for the cardiovascular system were mainly caused by drug–drug interactions, which were in most instances not of direct clinical relevance. In daily practice, high numbers of drug–drug interactions are seen within this group, and many problems caused by these interactions will be prevented by regularly measurements (such as potassium levels or blood pressure).[23–24]

Recommendations regarding medicines for the respiratory tract were mainly aimed at the suitability of inhalation devices used for older patients. This is consistent with other studies that also found that older patients frequently have problems taking inhaled medication,[25,12] therefore such a signal to the physician may be relevant.

Most points of attention of direct clinical relevance were seen in the group of medicines for the central nervous system, which were in particular related to benzodiazepine use. Problems included the use for an incorrect period, in dosages exceeding the geriatric daily dosage and use of substances with a long half-life time that are not suitable for use in older patients. Prolonged use of hypnotics, particularly in the elderly, is a widespread problem, as numerous studies concerning inappropriate prescribing for the elderly have shown.[13,14,20,26]

In almost two thirds of the patients, prescribing omissions were identified, of which one out of four were of direct clinical relevance. Prescribing omissions are only scarcely described in studies concerning inappropriate prescribing for the elderly,[27] in spite of studies that prove that a substantial number of older patients is not receiving omitted but necessary pharmacotherapy for established diagnosis.[28–31] Prescribing omissions may place older patients at higher risk for preventable adverse consequences. Hence, medication reviews should point at the quality of complete medication profiles and not only at the quantity of drugs prescribed.

Implications for future research or clinical practice

Over half of detected points of attention recurred in only a handful of drug classes, suggesting that medication reviews of older outpatients on polypharmacy may benefit from a computerised screening tool. Although such a computerised screening tool could detect a large proportion of potential problems, the detection of various other problems in our analysis shows that such a tool should be supplemented with a more implicit method of assessment. The professional judgement of a complete medication profile by an experienced healthcare provider can detect problems that would go unnoticed if one would rely solely on computerised screening. The overall κ-value indicated slight agreement after the round in writing. All panel members seemed to have their own speciality. During the consensus meetings, however, consensus about all aspects was reached. In some instances panel members had to make out their case, in other instances consensus was reached quickly because other panel members realised they had overlooked a particular problem. Another interesting observation (data not shown) was that about 15% of the points of attention could only be detected because the panel was not only supplied with the medications prescribed but also with the reasons for prescribing them. Together these findings raise the possibility that medication reviews ideally should be performed by more

than one healthcare professional, ideally of different professions, with the medical record at their disposal. Further research is needed to confirm these assumptions.

All in all, we conclude that it appears advisable to perform medication reviews for home-dwelling older patients by GPs, community pharmacists and other specialists. It yields significant numbers of relevant prescription-related points of attention and a potential for quality improvement of prescriptions for older patients living in the community.

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Chapter 4

A composite screening tool for medication reviews of outpatients; General issues with concrete examples

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Abstract

The regular performance of medication reviews is prominent among the methods that are advocated to reduce the extent and seriousness of drug-related problems, such as adverse drug reactions, drug-disease interactions, drug-drug interactions, drug ineffectiveness and cost-ineffectiveness. Several screening tools have been developed to guide practising healthcare professionals and researchers in reviewing the medication patterns of elderly patients, but each of these tools has its own limitations. This review offers a wide range of presciption-related, treatment-related and patient-related issues that should be taken into account in the implicit reviewing of medication patterns. A broad selection of concrete examples and references that can be used as basis for the explicit screening of medication patterns in outpatients is also offered.

Patients on repeat prescriptions are at risk of experiencing adverse drug reactions, drug-disease interactions, drug-drug interactions and ineffectiveness, particularly when they are elderly. This is due to factors such as polypharmacy, suboptimal monitoring, nonadherence, and pathological or age-related physiological changes. The regular performance of pharmacy-initiated medication reviews is prominent among the methods that are advocated to reduce the extent and seriousness of such problems.[1-3] Drug treatments should be periodically reconsidered in terms of their adverse effects. Randomized controlled trials have partially confirmed that pharmacy-initiated medication reviews may have economic as well as clinical benefits, if designed and executed appropriately.[1;2;4-10]

In several countries, pharmacists can now claim a fee for conducting medication reviews of outpatients. Australian community pharmacists are compensated for home medicines reviews under an agreement between the government and the pharmacy guild. In cooperation with a general practitioner (who refers the patient), the pharmacist visits the patient at home, reviews his or her medications, and provides the general practitioner with a report. The general practitioner and patient then agree on a medication management plan. The pharmacist's responsibilities vary, depending on whether he of she is accredited to conduct medication reviews.[11] In The Netherlands, private health insurance companies have recently started to pay a fee to community pharmacists for conducting medication reviews of outpatients on polypharmacy.[12;13]

In the UK, The UK Task Force on Medicines Partnership distinguishes four different levels of medication reviews (Table 1). Pharmacists in this country are allowed to claim payment for so-called medicines use reviews, which aim at improvement of the patient's knowledge and use of drugs by in particular: (a) establishing the patient's actual use, understanding and experience of taking drugs; (b) identifying, discussing and resolving poor or ineffective use of drugs by the patient; (c) identifying side effects and drug

interactions that may affect the patient's compliance with instructions given to him by a health care professional for the taking of drugs; and (d) improving the clinical and cost effectiveness of drugs prescribed to patients thereby reducing the wastage of such drugs.[15]

1. Objectives

The growing importance of medication reviews increases the need for adequate guidance on how to perform such reviews, particularly in elderly patients with complicated drug regimens. The present paper examines prominent existing tools for medication reviewing and then presents a new composite tool which supplies:

1. various general issues that should be taken into account in the implicit reviewing of medication patterns;
2. a broad range of concrete examples and detailed references to examples that can be used for the explicit reviewing of medication patterns.

2. Methods

Our initial search strategy for finding pertinent articles was a free text search on "medication review" OR "medication reviews" in Medline through on-line consultation of PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed; entrez date up to Dec 31 2006). We resorted to this free text approach, because Pubmed did not provide a specific MeSH term for medication review. Only 141 references were retrieved, many of which were judged (on the basis of their title and/or abstract) to be less useful for our purposes. More importantly, the search failed to unearth various relevant articles that we had uncovered in the course of an earlier literature review on repeat prescribing in ambulatory care patients[2] and two original studies of prescriber-related and user-related drug-related problems in elderly outpatients on polypharmacy.[16;17] We therefore supplemented our initial Medline search with an incremental search strategy that comprised the following elements:

1. Manual searching of the literature that had already been collected or consulted for our earlier studies.[2;16;17] As these studies had focused on ambulatory care patients, we decided to give our new study the same focus.
2. On-line searching for additional papers of the research groups that turned out to be prominent in the field of medication reviews and related issues.
3. Manual searching of the bibliography of every useful reference retrieved for additional references and iterating this procedure until no more useful references emerged.

3. Existing screening tools

Several implicit and/or explicit screening tools have been developed to guide practising healthcare professionals as well as drug utilization researchers in reviewing the medication patterns of elderly patients, but each of them has its own benefits and limitations. This will be illustrated by discussing some prominent examples below. Generally speaking, implicit screening criteria allow a full and flexible clinical judgement of individual drug treatments, which can also detect problems that are not prespecified. However, implicit screening methods depend heavily on the knowledge, experience and skills of the individual reviewer. They may be relatively time-consuming and it can be difficult to apply them consistently and to measure outcomes in a valid and reliable way. In contrast, explicit screening criteria have the advantages that they can be reliably based on literature review and expert consensus, that they can identify and prioritize problems in a consistent way, and that they can be easily incorporated in practice computer systems. However, explicit screening methods have the disadvantage of an inflexible approach, which leaves insufficient room for individual differences between patients and can thereby lead to false positive signals (i.e., the signaling that a drug-related problem exists whereas in reality it does not exist). Furthermore, explicit screening methods will miss any drug-related problem that has not been prespecified and will therefore fail to provide a full assessment of the patient. All in all, the combination of implicit and explicit methods can be expected to offer a more thorough assessment than each approach separately. The only caveat is that such a combined application can be more time-consuming and care should therefore be taken to keep this approach sufficiently feasible in daily practice.[18]

3.1. Beers criteria

A widely advocated explicit screening tool was introduced in 1991 by Beers and associates.[19] It was first developed to be used in nursing home patients and consists of a list of concrete drugs and drug classes which should generally be avoided in elderly patients. These so-called Beers criteria have been very useful for assessing medication appropriateness in elderly populations, and they have been widely used for this purpose.[20-23] When interpreting such data, one should realise that some drugs on the Beers list are appropriate for specific patients in certain circumstances.[24;25] Furthermore, the original Beers criteria focused entirely on the appropriateness of medications in elderly patients without addressing other important categories of drug-related problems. In 2003, an additional Beers list was introduced that specified certain drug-disease combinations which should also generally be avoided in elderly patients.[26] While this broadened the scope of the Beers criteria, it certainly did not result in a complete set for medication reviewing.

3.2. Medication Appropriateness Index

A well-known example of an implicit screening tool for reviewing medication patterns in elderly patients is the so-called Medication Appropriateness Index.[27-29] The first version was published in 1992 by Hanlon and co-workers[30] and a modified version was presented by the same group in 1997.[31] The Index raises a number of important issues that are not or incompletely considered by the Beers criteria: has each medication an indication; is it expected to be effective for the patient's condition; is each dosage correct; are the directions for use correct and practical; are there any clinically significant drug-drug interactions or drug-disease interactions; is there any unnecessary duplication with other drugs; is the duration of therapy acceptable; and is each medication the least expensive alternative compared with others of equal utility. Contrary to the Beers criteria, the Medication Appropriateness Index does not specify, which drug therapies or drug combinations are of primary concern in these domains. Furthermore, even the Medication Appropriateness Index does not cover *all* relevant categories of drug-related problems. For instance, it does not address such important issues as adherence to each medication regimen[7] or the risk that the patient is not receiving a required medication.[32;33]

3.3. ACOVE indicators

The so-called ACOVE indicators for Assessing Care Of Vulnerable Elders offer a mix of explicit and implicit screening criteria. In 2001, a series of consensus-based sets of ACOVE indicators were published as a special issue of the Annals of Internal Medicine. A few years later, the results of applying these indicators to assess the quality of medical care and pharmacological care for vulnerable elders were presented in the same journal.[34;35]

One of the ACOVE sets of indicators focuses on appropriate medication use. It consists of 12 different indicators, which range from very specific topics (e.g., avoid barbiturates, if they are not needed to control seizures; check electrolytes within 1 week of initiating therapy with a thiazide or loop diuretic and at least annually thereafter) to very broad recommendations (e.g., every new drug should have a clearly defined indication; the patient or caregiver should receive education for every new drug about its purpose, how to take it, and expected side effects; every vulnerable elder should have a drug regimen review at least annually – *sic!*).[32] In addition, various drug therapy-related indicators occur in the other ACOVE sets of indicators.[36] An example are recommendations in the set for the management of osteoarthritis to use acetaminophen as the first drug and to give this drug in a maximum dose (considering age and comorbidity) before switching to another agent.[37]

Although the ACOVE indicators point out some important aspects of drug therapy in the elderly that are neither covered by the Beers criteria nor the Medication Appropriateness

Index (e.g., the risk of underprescribing and the need to monitor certain drug therapies carefully), neither their range of general drug-related topics nor their selection of drug-specific indicators provide an exhaustive enumeration.

4. General issues in implicit screening

Based on our earlier review of the quality management of repeat prescriptions,[2] two original studies of user-related and prescriber-related problems in elderly outpatients on polypharmacy,[16;17] and various other papers about general aspects to be considered when reviewing medications,[3;14;18;26;31;32;36;38-44] we identified a large number of issues that should be taken into account in the implicit screening of medication patterns in outpatients.

Following the classification of medication reviews by the UK Task Force on Medicines Partnership (Table 1), we divided these issues into presciption issues, treatment issues and patient issues (Table 2). The next sections will outline these categories one by one, identify the general issues in each category, and supplement each general issue with concrete examples and/or detailed references to concrete examples.

Table 1 Levels of medication review distinguished by the UK Task Force on Medicines Partnership (reproduced with permission from its 2002 report Room for Review[14])

Level	Description
0 Ad-hoc review	*Unstructured, opportunistic review of a patient's medication* E.g., an isolated question to a patient from a receptionist in the surgery or from a pharmacist in the community pharmacy.
1 Presciption review	*Technical review of list of patient's medicines* This can be helpful in identifying anomalies and highlighting patients who may need clinical medication reviews, but as a stand-alone tool its benefits are relatively limited as it does not normally allow for a full discussion with the patient. Examples of interventions: include dose and pack optimisation, resolving quantity problems, drug presentation issues, and brand to generic switches.
2 Treatment review	*Review of medicines with patient's full notes* This normally takes place under the direction of a doctor, nurse or pharmacist, but often without the patient – e.g., removal of unwanted items from the repeat medicines list, and dose adjustments. It may include the complete repeat prescription or focus on one therapeutic area (eg hypertension), drug (eg lithium) or group of drugs (eg NSAIDs). Recommendations may be passed to the prescriber for implementation. Examples of outcomes: reducing the number of items, modifying doses.
3 Clinical medication review	*Face-to-face review of medicines and condition* This requires access to the patient's notes, full record of prescriptions and non-drug care and results from laboratory tests etc. It should include the complete repeat prescription as well as over-the-counter and complementary remedies. In a clinical medication review, medicines are not examined in isolation but considered in the context of the patient's condition and the way they live their lives. The review should involve the patient as a full partner (i.e., listening to the patient's views and beliefs about his medicines, reaching an honest understanding of his medicine taking behaviour, and taking full account of his preferences in any decisions about treatment. The invitation to a review should include both the patient and (when appropriate) the carer. A level 3 review involves evaluating the therapeutic efficacy of each drug, identifying and addressing unmet therapeutic need, monitoring the progress of the conditions being treated, together with purposeful discussion about specific aspects of the patient's medication to facilitate a concordant approach to medicine taking. Clinical medication review may take place in a variety of settings including the patient's home.

5. Perscription issues

Prescription issues often focus on cost reduction. While cost effectiveness is a legitimate objective of medication review, it should always be subordinate to improved care and safety.[14]

5.1. Generic substitution

Consider the possibility that medications may be substituted by cheaper generic equivalents

Generic substitution, which involves the substitution of a medication by a cheaper medication with the same active ingredient(s), drug strength(s) and dosage form, can offer substantial economic benefits.[45;46] It can usually be performed safely, if sufficient attention is paid to the following caveats:[47-49]

- The risk of inequivalence is smaller, when drug licensing authorities verify systematically and rigorously that generic products are bioequivalent to original brand products and to each other and it is larger, when this is not the case.[48]
- The risk of inequivalence depends on the specific dosage form and specific drug substance. Caution is especially needed when the dosage form has controlled-release properties[50-52] and when the drug substance has a narrow therapeutic index (e.g., anticonvulsants, warfarin.[53;54]
- Alertness to the occasional possibility that an individual patient is confused by differences in outward appearance (e.g., colour, shape, packaging) or in content of the package insert.[55] A particular concern is the risk of confusion between original brands and parallel imported equivalents with different brand names.

5.2. Therapeutic substitution

Consider the possibility that medications may be substituted by cheaper therapeutic equivalents

A step beyond generic substitution is class substitution, in which medications are replaced by cheaper medications with another substance from the same drug class. This type of substitution is a pillar under many drug formularies and reference pricing systems, and the potential cost savings often seem larger than what can be achieved by generic substitution.[56;57] However, the pharmacotherapeutic caveats that should be respected to guarantee therapeutic equivalence are also of a different order. Drug substances with the same mechanism of action may still be different with respect to ancillary pharmacological properties, safety profile and/or the risk of drug-drug interactions, which may lead to differences in effectiveness, safety, or applicability.[58;59;60] For instance, there is substantial evidence to suggest that beta-blocking agents are not always equal with respect to their

effectiveness[61-63] and that the classical NSAIDs show notable variation in their adverse reaction profiles.[64;65] An additional concern is that studies on clinical endpoints are usually not available for all drug substances belonging to the same cardiovascular drug class. Even if one assumes that the effects on cardiovascular endpoints are class effects, it may be difficult to ascertain which dose levels are appropriate for those substances which have not been evaluated in endpoint trials. This is especially a problem, when monitoring on the basis of a pharmacological effect (e.g., on cholesterol level or blood pressure) is either impossible or inadequately executed.[60;66]

6. Treatment issues

The reason for prescribing should be known to the medication reviewer

A general point with respect to treatment issues is that medication reviewers may identify and evaluate certain types of problems only or much easier, when they do not only have access to the pharmacy record but also to the medical record. In a recent UK evaluation of pharmacist-led medication reviews in patients over 65, the pharmacists detected 18% of the drug-related problems by reviewing medical notes (in addition to 52% by looking at perscription records and 29% by interviewing patients at home).[67] Evidence that the quality of a pharmacist-conducted medication review increases, as access to complete patient information increases, also comes from a US study of paper cases.[68]

6.1. Potentially superfluous medications

Consider discontinuation of medications without well-established effectiveness

Examples of medications with marginal or questionable effectiveness include:

1) hydergine and piracetam for dementia or cognitive impairment[69;70];
2) betahistine for Meniere's disease[71]; most oral vasodilators for intermittent claudication[72;73];
3) antispasmodic or anticholinergic agents in irritable bowel syndrome[74];
1) expectorants for acute bronchitis[75;76];
2) long-term use of low-dose oral corticosteroids for stable chronic obstructive pulmonary disease (COPD)[77];
3) most phytotherapeutic agents for most indications[78;79] and homeopathic agents for any indication.[80;81]

Consider discontinuation of medications without effectiveness and/or valid reason for use in the particular patient under review

Many medications may be stopped in elderly outpatients without the occurrence of an adverse drug withdrawal event. However, such withdrawal events are known to occur, and

if they do, they result in substantial health care utilization. One should therefore be vigilant for disease recurrence, when drug therapy is discontinued in the elderly.[82;83] A concrete list of drugs that qualify for careful consideration of their discontinuation in the elderly has been drawn up by Woodward.[41] Well-known examples include:

1. Loop diuretics. In a study evaluating their use in Dutch community-dwelling patients aged 75 years or older, general practitioners considered their continuation unnecessary in 19.5% of the patients. The reason for their use was unknown in 8% of the patients, and they were used for the controversial indication of ankle edema in another 8%.[84]
2. H_2-antagonists and proton pump inhibitors. Studies in general populations have shown that these acid suppressants are not always used for a valid reason[85;86] and that an appreciable proportion of chronic users is able to discontinue these drugs.[87;88] A recent epidemiological study suggests that use of proton pump inhibitors for more than a year is associated with an increased risk of hip fracture in elderly users, possibly by interference with calcium absorption.[89]
3. Cholinesterase inhibitors and memantine. As these agents produce clinically relevant effects only in a minority of patients with Alzheimer's disease,[90;91] it is important to assess after initiation of therapy which patients respond and which patients do not.[92]
4. Anticholinergic medications for the treatment of overactive bladder,[41] because their clinical benefits may be of questionable significance in many patients.[93]
5. Antihypertensive medications in very old patients. The benefits and risks of these agents in patients over 80 years of age are still insufficiently clear.[94-96] Preliminary results of a controlled trial in this age group suggest that the risk of stroke may be reduced but that this gain may be offset by extra non-stroke deaths.[97] Trials to withdraw or lower the dosage of antihypertensive medications in elderly outpatients have shown that this may be successful in up to 40% of the patients, when combined with salt restriction and weight loss.[94]
6. Oral mucolytics. A recent review suggests that treatment with these agents is not cost-effective in all patients with chronic bronchitis or COPD and that it should be restricted to patients with more frequent and severe exacerbations.[98]

Consider the possibility of potentially inappropriate duplication of drug treatment

Unnecessary duplications of drug treatment (different brands of the same drug or different drug substances from the same therapeutic class) should be avoided.[99;100] For instance, the concurrent use more than one nonsteroidal anti-inflammatory drug (NSAID) may increase the risk of gastroduodenal toxicity.[101]

A particular risk of unnecessary duplication may occur, when drug substances or preparations with the same pharmacological effects are applied for different therapeutic

reasons, e.g., alpha-blocking agents for hypertension and benign prostatic hyperplasia, or norepinephrine/serotonin reuptake inhibitors for depression and urinary incontinence.[102] A particular risk moment for drug duplication is the period immediately after discharge of patients from hospital.[103]

Consider the possibility that one or more medications may have been added to an existing drug therapy to combat an adverse effect of one or more medications already taken

A new medication may be added to an existing drug regimen to combat an adverse drug reaction. This so-called "prescribing cascade" may place the patient at risk of developing additional adverse effects relating to this potentially unnecessary treatment. Examples include the addition of:[104;105]

- An antihypertensive to NSAID therapy (because of a rise in blood pressure);
- Levodopa to metoclopramide treatment (because of parkinsonian symptoms);
- An acid suppressant drug to a nitrate or calcium channel blocker (because these latter drugs may precipitate gastroesophageal reflux by decreasing lower esophageal sphincter pressure);[106]
- A cough suppressant to treatment with an ACE inhibitor (because of a dry persistent cough[107]);
- A cholinesterase inhibitor to drug treatment capable of impairing cognition;[108]
- An anticholinergic drug to medications which are capable of inducing urinary incontinence,[109;110] such as cholinesterase inhibitors for the treatment of dementia.[111;112] The possibility that drug-induced urinary incontinence may have triggered the addition of an absorbent incontinence product should also be considered.[113]
- A drug for benign prostatic hyperplasia to anticholinergic medications (to combat urinary hesitation[114]).

In such cases, it should be evaluated whether the causative drug can be withdrawn or substituted with another medication that does not have the same adverse effect.

In the past, the addition of an antigout agent to a thiazide diuretic was also commonly listed as an example, but a recent study has cast doubt on the validity of the underlying assumption that thiazide diuretics actually increase the risk of gout.[115]

6.2. Potentially inappropriate medications

Consider elimination of medications that are potentially inappropriate for the patient under review (e.g. because of the patient's age or because a side effect has developed)

Since adverse drug effects can have profound clinical and economic consequences for elderly patients, Beers and associates have identified a large number of drugs and drug

classes that should generally be avoided in the elderly (cf. paragraph 3.1).[19;116] The reader is referred to Table 1 in the 2003 update of these soc-alled Beers criteria for the most recent version.[26] A few comments are in order. Firstly, the reasons for including nitrofurantoin (potential for renal impairment and availability of safer alternatives) are incorrect.[117] It is only true that nitrofurantoin should not be given to patients with renal impairment, since antibacterial concentrations in the urine might not be attained, whereas the risk of toxicity (peripheral neuropathy, hepatic reactions) is increased.[102;118;119] Secondly, the Beers criteria should not be applied indiscriminately, because there may be acceptable reasons, why some of the listed medications are prescribed to elderly patients (e.g., low-dose amitriptyline in neuropathic pain.[120]) Thirdly, the Beers listing is not without omissions, if only because it focuses on the medications that are available in the United States. Prominent examples of medications that are excluded but should nevertheless be considered as potentially inappropriate for the elderly are:

1) glibenclamide, because its long duration of action can result in prolonged and recurrent hypoglycemia in elderly patients[121-123];
2) theophylline (unless its plasma levels can be closely monitored), because it has a narrow therapeutic index and because its plasma level is sensitive to reduced clearance, underlying diseases and drug-drug interactions[124-126];
3) quinine and hydroquinine, especially when used longer than a few weeks, because their modest and variable effects on restless legs or nocturnal muscle cramps are outweighed by the risk of adverse reactions, such as cinchonism, thrombocytopenia and hemianopsia.[102;127-129]
4) Atypical antipsychotics in higher doses, which entail a risk of serious adverse reactions in the elderly and in certain conditions (e.g., Parkinson's disease, dementia).[130-132]

6.3. Potentially inappropriate dosages

Consider whether the dosage of each medication is still appropriate

Compared to the young, elderly patients show a more marked variability in hepatic and renal function, and this may be accentuated by differences in intake of food, co-medications and pharmacogenetic influences. Furthermore, elderly patients may have altered sensitivity to anticoagulants, cardiovascular drugs, and psychotropic drugs at the pharmacodynamic level.[133-136] As a result, individual elderly patients may need reduced dose levels so that an initially correct dosage may become less appropriate.[25;137;138]

The need to explore lower doses is particularly relevant for medications with a narrow therapeutic index, such as lithium,[139] digoxin,[140] theophylline,[141] metoclopramide,[142] tricyclic antidepressants,[143] antipsychotic agents[144] sulphonylurea agents,[121] dopaminergic antiparkinson agents, sedating antiepileptics, opioid analgesics and verapamil.[145;146]

Adjustment of drug dosages to an appropriate geriatric level can also be relevant in the absence of a narrow therapeutic index. It has been repeatedly observed, for instance, that high dose levels of benzodiazepines in elderly users are associated with an increased risk of hip fractures.[147;148]

When low-dose therapy is considered in elderly patients, care should be taken to avoid that concerns about side effects lead to an inappropriately low dosage.[133;149] This risk is illustrated by a North American study, which evaluated patterns of prescription of warfarin in frail older people with atrial fibrillation and found that INR levels were maintained below the established therapeutic range in 45% of the patients.[150]

When prescribing and dispensing specific geriatric dosages, it should be realized that elderly patients may find it difficult to split tablets into two equal halves, even when these tablets are provided with a score line. Tablets that already provide the lower dose without splitting are therefore preferable.[151;152]

6.4. Potentially inappropriate duration of treatment

Consider whether medications are prescribed for an inappropriately long period

Repeat prescribing without direct doctor-patient contact entails the risk that there is no longer adequate control that every repeat prescription is still appropriate, effective and well-tolerated, and that it is still being viewed upon and taken by the patient as intended.[2] In a recent US study, excessive duration of drug therapy was one of the five top reasons for interventions by pharmacists, which accounted for almost 10% of all interventions.[153] A special problem with repeat prescribing is that general practitioners (GPs) frequently continue drug therapies which have been initiated by medical specialists. Although GPs often indicate that this particular part of their prescribing behaviour cannot be changed, they have their own responsibility, when repeating specialist-initiated prescriptions.[2]

Prolonged use of antibacterials can be justified for certain indications (e.g., tuberculosis or long-term prophylaxis of urinary tract infections), but it may be unadvisable in other situations. For instance, repeating antibiotic prescriptions for a lower respiratory tract infection should be the exception rather than the rule in general practice.[154] Likewise, the suggested duration of treatment with an oral anticoagulant after venous thromboembolism varies from 5 weeks to indefinite, depending on the type of event and patient-bound risk factors.[155]

The Beers criteria advise against the long-term use of stimulant laxatives (e.g., bisacodyl, cascara sagrada), except in the presence of an opioid analgesic, and against the long-term use of a fully dosed non-selective NSAID with a longer half-life (e.g., naproxen, oxaprozin, piroxicam).[26]

Long-term anxiolytic or hypnotic use of benzodiazepines and related substances is limited by serious problems of dependence. Continuation of such use without any attempt of drug withdrawal or dose reduction should generally be discouraged.[156;157] Strategies for discontinuation can be divided into gradual discontinuation programs and minimal interventions. The former may be successful in two-thirds of patients from general populations, but they are labour-intensive, as they involve gradual tapering of dosage to minimize the risk of withdrawal symptoms.[158;159] Minimal intervention strategies invite patients to stop on their own or to come around for an evaluation consultation (e.g. by a letter making them aware of the risks involved). This type of intervention is much less labour-intensive, and it is successful in about one fifth or one quarter of patients from general populations.[158;160]

Consider whether medications have been prescribed for an inappropriately short period

The prescription period of medications should not be too short either. For instance, patients with major depression should receive antidepressant treatment for at least 3-6 months after an initial response to decrease the risk of relapse or recurrence.[161;162] It should be realized, however, that a medication review is not an optimal method for assuring an adequate minimal treatment period, since it can only identify cases retrospectively, after the use has already been discontinued.

See also the comments on drug persistence in the paragraph 7.2.

6.5. Drug-disease interactions

Consider the risk of potentially inappropriate drug-disease interactions

For listings of drug-disease interactions that are potentially harmful for elderly patients, the reader is refererred to McLeod et al.[163] and Fick et al.[26] The occurrence of such drug-disease interactions in elderly patients in the US has been studied by Lindblad et al.[164] and Zhan et al.[165] A particular concern in this domain is that strict adherence to current clinical practice guidelines (CPGs) may have undesirable effects, when caring for elderly patients with several comorbidities. Boyd et al.[166] constructed a hypothetical 79-year-old woman with five chronic diseases (osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension, and chronic obstructive pulmonary disease) and discovered that concurrent adherence to all five CPGs for these diseases in the US resulted in potential interactions between a medication and a disease other than the target disease, between medications for different diseases, and between food and medications. They also found that recommendations could also contradict one another. If the hypothetical osteoporotic, diabetic patient would have had peripheral neuropathy, the osteoporosis CPG recommended that she perform weight-bearing exercise, while the diabetes CPG cautioned

that some patients with advanced peripheral neuropathy should avoid weight-bearing exercise.

When clinical information is not available, concurrently used medications may serve as more or less suitable surrogate markers of disease states, e.g. insulin for diabetes mellitus,[167] nitrate prescriptions for ischaemic heart disease,[168] and digoxin or amiodarone for atrial fibrillation.[40]

Medication reviewers should bear in mind that contraindications may arise long after a chronic drug therapy has been established.[169] One reason is that the health status of the patient can change over time, e.g. because new co-morbidity develops or because the patient has grown much older than he was at the start of the treatment. For a US list of specific drug-disease combinations that should generally be avoided in the elderly, the reader is referred to Table 2 in the most recent version of the Beers criteria.[26]

Table 2. General issues in the implicit screening of medication patterns in outpatients

Prescription issues
- Consider the possibility that medications may be substituted by cheaper generic equivalents
- Consider the possibility that medications may be substituted by cheaper therapeutic equivalents
Treatment issues
- The reason for prescribing should be known to the medication reviewer
- Consider discontinuation of medications without well-established effectiveness
- Consider discontinuation of medications without effectiveness and/or valid reason for use in the particular patient under review
- Consider the possibility of potentially inappropriate duplication of drug treatment
- Consider the possibility that one or more medications may have been added to an existing drug therapy to combat an adverse effect of one or more medications already taken
- Consider elimination of medications that are potentially inappropriate for the patient under review (e.g. because of the patient's age or because a side effect has developed)
- Consider whether the dosage of each medication is still appropriate
- Consider whether medications are prescribed for an inappropriately long period
- Consider whether medications have been prescribed for an inappropriately short period
- Consider the risk of potentially inappropriate drug-disease interactions
- Consider the risk of potentially inappropriate drug-drug interactions
- Consider the risk of potentially inappropriate duplication of adverse effects
- Consider the possibility that a required medication is inappropriately missing
- Consider the appropriateness of drug treatment in the light of organ functions, such as renal and hepatic function
- Consider the appropriateness of drug treatment in the light of electrolyte levels
- Consider the appropriateness of drug treatment in the light of pharmacogenetic test results
Patient issues
- Direct contact between reviewer and patient (or caregiver) offers essential advantages
- Ask the patient what he knows about his medications and condition(s), which medications he actually takes and how he takes them, which beneficial and unwanted effects he experiences, and which queries the patient has himself
- Make adequate room for the patient perspective
- Consider the possibility that the patient is taking less of the medication(s) than prescribed
- Consider the possibility that the patient is taking more of the medication(s) than prescribed
- Consider earlier patient experiences with drugs
- Consider special patient characteristics and habits
- Consider the need of special packaging
- Consider whether the patient is able to self-administer dosage forms that require special skills

A new contraindication may also develop when a drug turns out to be less safe than it was initially assumed to be. For instance, it has recently become clear that COX-2 inhibitors carry such cardiovascular risks that they should not be used in patients with established ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease, and that caution should be exercised when prescribing these agents to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, diabetes and smoking.[170]

Medication reviewers should pay special attention to the asssessment of relative contraindications, which are not strictly forbidden but require careful follow-up to avoid unnecessary adverse consequences. A medication review also offers the opportunity to check whether any contraindicated drug-disease combination that should already have been avoided before the patient started the therapy may nevertheless have been allowed to pass.

6.6. Drug-drug interactions

Consider the risk of potentially inappropriate drug-drug interactions

For general background information, the reader is referred to textbooks in this domain.[171-173] Medication reviewers should be aware that pharmacists have a tendency to assess the risk of a drug-drug interaction most thoroughly, before that combination is dispensed for the first time.[174] There are also drug-drug interactions, however, that do not require strict avoidance but should be carefully monitored to prevent adverse consequences (see Table 3 for a selection).

Medication reviewers may also check whether any drug-drug combination has been allowed to pass, which should have been intercepted before it was started. Malone et al. carefully developed a list of 25 clinically important drug-drug interactions that are likely to occur in outpatients and should be avoided as much as possible.[176] Application of this selection to a large US prescription claims database revealed that 0.8% of the patients had been exposed to a drug-drug interaction on the list. The highest prevalence (278.56 per 100,000 persons) and highest case-exposure rate (242.7 per 1,000 warfarin recipients) was found for warfarin plus a nonsteroidal antiinflammatory drug.[177] Other publications also highlight the need for checking on contraindicated drug combinations[163;165;178-180] as well as the reasons why they are not always prevented in daily practice.[181;182]

Table 3. Examples of drug-drug combinations that do not require strict avoidance but should be followed up carefully to prevent adverse consequences (after De Gier 2006)[175]

Drug-drug combination	Potential risk	Follow-up required
Digoxine + Loop diuretics or thiazide diuretics	Increased toxicity of digoxin	Monitoring of potassium level
Sulphonylurea derivatives + chloramphenicol	Increased effect of sulphonylurea derivative	Monitoring of glucose levels
Methotrexate + salicylates or NSAIDs	Increased level of methotrexate and risk of decreasing renal function	Monitoring of renal function, hepatic function and blood picture
Potassium-sparing diuretics + potassium supplements	Increased plasma level of potassium	Monitoring of potassium level
Hypoglycaemics + isoniazid	Decreased glucose tolerance	Monitoring of glucose levels
NSAIDs + ACE inhibitors or angiotensin II receptor antagonists	Decreased effect of ACE inhibitor or angiotensin II receptor antagonist; in patients with heart failure, addition of an NSAID may lead to deterioration of renal function and an increased potassium level	Depending on indication of ACE inhibitor or angiotensin II receptor antagonist: - *hypertension*: monitoring of blood pressure - *heart failure*: monitoring of symptoms (also by patient)
Beta-blocking agents + NSAIDs	Decreased antihypertensive effects of beta-blocking agent	Monitoring of blood pressure (if NSAID is used for longer period)
Loop diuretics + NSAIDs	Decreased effect of loop diuretic	In heart failure: monitoring of symptoms (also by patient), renal function and potassium level
ACE inhibitors or angiotensin II receptor antagonists + potassium-sparing diuretics or potassium supplements	Increased plasma level of potassium	Monitoring of potassium level
HMG-CoA-reductase inhibitors + ciclosporin, tacrolimus or fibrates	Risk of myopathy and rhabdomyolysis	Combined use only under strict specialistic monitoring
Corticosteroids + enzyme inductors	Decreased plasma level of corticosteroid	Adjustment of corticosteroid dosage based on clinical picture

Consider the risk of potentially inappropriate duplication of adverse effects

Drugs from different drug classes may potentiate each other, particularly in the elderly, when they have similar adverse effects:

1. Renal impairment; ACE inhibitors, NSAIDs and diuretics can all impair renal function. The demonstrated advantages of these medications should therefore be carefully balanced against the risk of inducing renal failure by combining them.[183-186;187] Such caution is also warranted with respect to angiotensin receptor antagonists[187] and Cox-2 inhibitors.[188;189]
2. QT-interval prolongation;[190;191]
3. Anticholinergic effects;[111;192;193] significant serum anticholinergic activity has also been reported for drugs, for which this was not expected, such as theophylline, prednisolone, and cimetidine;[194]
4. Dizziness, drowsiness, and the risk of falls.[195-197] Recent studies suggest that certain drugs increase the risk of falls in a modifiable way that is independent of comorbidity.[198;199] Centrally active drugs which have been associated with an increased

risk of falls in the elderly include: anxiolytics, sedatives/hypnotics, antipsychotics, antidepressants, and anticonvulsants.[197;200;201] Short half-life benzodiazepines are not safer in this respect than long half-life benzodiazepines.[197;201;202] An important cardiovascular drug class which has been associated with falls in the elderly is the class of type Ia antiarrhythmics,[203] and the risk that diuretics can cause dizziness as a consequence of orthostatic hypotension should also be taken into account.[198]

5. Confusion or delirium;[204;205]
6. Constipation.[114;206]

6.7. Undertreatment

Consider the possibility that a required medication is inappropriately missing

Even when patients are already on polypharmacy, they do not always receive all the drugs that are indicated in their condition.[16;33;207-209] Examples of missing drugs include:

1. Acetylsalicylic acid should always be considered in patients with angina pectoris;[210;211]
2. Patients on high daily doses of corticosteroids often need a bisphosphonate to protect them against osteoporosis;[212;213]
3. Laxative therapy is often needed to treat or prevent opioid-induced constipation;[214]
4. Elderly users of NSAIDs may need gastroprotective agents, if the NSAID cannot be ceased.[215-217]
5. Elderly and demented patients with chronic pain may need opioids.[218;219]
6. Insulin therapy is not only a treatment option for younger patients with type 2 diabetes but also for elderly patients with this disease.[220]

There is increasing evidence that elderly populations may benefit as much from certain cardiovascular drug therapies as younger adults do, which increases the range of medications which may be missing. Relevant examples include:

1. Not only middle-aged patients but also patients over 70 years of age can benefit from statin treatment;[221;222]
2. ACE inhibitor use was associated with a significant survival benefit in a retrospective study of hospitalized older heart failure patients with perceived contraindications (hypotension, renal insufficiency, hyperkalemia, aortic stenosis);[223]
3. Warfarin treatment should not be withheld from elderly patients with atrial fibrillation who are at high risk of a stroke;[224;225]

When patients have several unrelated diseases concurrently, a particular concern is that one of these problems may consume attention at the expense of the other problems. There has been a Canadian study, for instance, which suggested that patients with diabetes mellitus are less likely to receive estrogen-replacement therapy, whereas patients with pulmonary emphysema are less likely to receive lipid-lowering medications.[226]

6.8. Use of laboratory test results

Increasing technological possibilities are making it more and more feasible for healthcare providers to access not only their own data file about a patient but also data about that specific patient which have been filed by other healthcare professionals. A particularly promising development in this field is better linkage between the pharmacy and the laboratory.[227] Pharmacy-initiated medication reviews are certainly among the pharmaceutical services which will benefit from an increased availability of laboratory test results. Clinical pharmacists have much experience, of course, with laboratory measurements of drug levels for therapeutic drug monitoring and establishing adherence. However, other types of laboratory data (e.g., blood lipid levels) can further improve the assessment of drug effectiveness and patient adherence. In addition, results from organ function tests, blood cell counts, electrolyte and enzyme determinations, etc., will greatly advance the evaluation of the drug safety issues that were raised in the preceding sections. For instance, concerns about the safety of digoxin in an elderly patient can be substantially mitigated by information about renal function.[228]

Consider the appropriateness of drug treatment in the light of organ functions, such as renal and hepatic function

As medication reviews are often performed in elderly patients, it is important that physiological changes in drug metabolism and excretion occur with ageing. Remarkably, the metabolic differences with younger adults are not characterized by a similar shift in all elderly people but with a sharp increase in the variation between individual patients.[134;229]

A quantitative estimate of renal function can be readily obtained by calculating creatinine clearance on the basis of serum creatinine, age, gender and weight of the patient. This calculated clearance can then be used to adjust the dosage or dosing interval of various renally cleared medications.[230;231] One should be aware that older patients may have impaired renal function despite normal serum creatinine levels and are therefore exposed to an increased risk of adverse reactions to hydrosoluble drugs.[232] There is evidence to suggest that, even when renal function data are available, they are not yet systematically applied for establishing the most appropriate dosage regimen.[227;233;234] Guidance for this type of adjustment can be found in package inserts and pharmacotherapeutic textbooks, but an important caveat is that such sources are not yet sufficiently evidence-based.[235;236]

Liver disease can also modify the kinetics of many drugs to an extent that dosage adjustment is required. While an analogous method for the simple and reliable quantification of hepatic clearance in daily practice is not available, high bilirubin level, or low albumin levels can provide qualitative evidence that a dose reduction for hepatically cleared medications is necessary.[227;237;238]

As the kidney and liver are important sites of drug toxicity,[189;239;240] renal and hepatic function data can also be applied to prevent the injudicious continuation of a nephrotoxic or hepatotoxic medication in patients with renal or hepatic impairment.

Besides renal and hepatic impairment, there are also other organ dysfunctions that can be recognised on the basis of laboratory test results and that can affect drug efficacy and drug safety.[241;242] For instance, it has been recognised for many years that thyroid disorders affect the pharmacokinetics of propranolol and can alter the sensitivity to digoxin, anticoagulants and sedatives.[243;244]

Consider the appropriateness of drug treatment in the light of electrolyte levels

Certain drug-related risks are substantially magnified by electrolyte abnormalities. For instance, hypokalemia predisposes for adverse reactions to digoxin[102] and the induction of torsade de pointes by such drugs as sotalol and psychotropic agents.[245;246] Conversely, many drugs are capable of inducing abnormal levels of sodium, potassium, calcium, magnesium, or phosphorus.[247-250] In recent years, there have been particular concerns about drug-induced hyponatremia[250;251] and hyperkalemia.[252;253] It has been demonstrated, for instance, that the addition of spironolactone to an ACE-inhibitor for heart failure entails a serious risk of life-threatening hyperkalemia, if potassium level and renal function are not closely monitored.[254]

Consider the appropriateness of drug treatment in the light of pharmacogenetic test results

Pharmacogenetic test data are likely to become more and more important for assessing and predicting drug efficacy and toxicity. This field started with a focus on polymorphisms of drug metabolism,[255;256] and it is precisely in this domain that practical possibilities to improve the dosing of certain drugs (phenytoin, antidepressants, mercaptopurine and azathioprine) are emerging or have already emerged.[257-261] Pharmacogenetics is rapidly expanding, however, to encompass a wide spectrum of genetic variations in pharmacokinetic and pharmacodynamic patient profiles.[262-264] While the practical application of this knowledge still largely lies in the future,[265;266] the moment that such data will become applicable within the framework of a medication review is coming more and more near. It is therefore important to design new systems for improving the availability of laboratory data to medication reviewers in such a way that pharmacogenetic test results can be taken into account.

In this development, pharmacogenetic parameters will only rarely represent a review issue in themselves (e.g., factor V Leiden mutation as a contraindication for the use of oral hormonal contraceptives[267]). More often, they will act as risk modifier in an already existing review issue, such as the appropriateness of:

- Drug choice (e.g., there is increasing evidence that the reponse to SSRIs is partially dependent on serotonin transporter promoter (SERTPR) polymorphism[268] and that antidepressant responses may also vary with other pharmacodynamic polymorphisms[269]; while it would be quite premature to determine such parameters in daily practice to predict clinical response, one day this might become a feasible reality);
- Dose regimen (see the examples given earlier in this paragraph);
- Drug-drug combination (e.g., allelic variants of CYP2C9 magnify the risk of an interaction between oral anticoagulants and NSAIDs[270]);
- Drug-herb combination (e.g., St. John's wort produces a significant increase in CYP2C19 activity in extensive CYP2C19 metabolizers but not in poor metabolizers[271]).

7. Patient issues

Direct contact between reviewer and patient (or caregiver) offers essential advantages

For a proper assessment of user-related issues, it is essential to combine the review of prescription records and/or medical records with an interview of the patient or caregiver to elucidate such aspects as actual medication taking behaviour and experiences of adverse effects.[2] In a UK intervention including a patient interview, such direct contact was considered most influential; potential changes were discussed with the patient to find out whether the patient would be intolerant of change. Agreeing suggested changes with the patient made implementation less time-consuming for the GP.[272] In a US study, 73% of the identified problems were recognized only through a patient interview.[273] In another US study, the longer the contact was between the reviewing pharmacist and patient, the more problems were identified and resolved; personal contacts identified and resolved more problems than contacts by telephone.[274]

7.1. Basic issues

Ask the patient what he knows about his medications and condition(s), which medications he actually takes and how he takes them, which beneficial and unwanted effects he experiences, and which queries the patient has himself

Important issues to be raised during the patient consultation include: does the patient know what the medications are for; does he remember the dosage of each medication; is he still taking each medication as prescribed; is he taking any other medications (including any complementary medicines); does he notice any benefits or side effects; and does the patient have any queries himself.[38] As outlined in the next paragraph, the last issue is certainly not the least important one.

Make adequate room for the patient perspective

Medication reviewers assessing the appropriateness of drug therapy should not restrict themselves to medical and pharmacological points of view, but should also incorporate the patient's perspective on appropriateness in their evaluation.[275;276] For instance, a physician prescribing drugs for an elderly patient may be primarily occupied with treating medically diagnosed diseases, whereas the patient is more interested in treatment that will reduce functional decline and disabilities.[277;278]

According to qualitative research of the patient perspective on medication reviews, patients and carers want to tell the reviewer about their personal beliefs, preferences and concerns, and they want to verify if they are taking the best medicines for their problems. To assure enough room for these needs, they would like to have time specifically set aside for the interview; someone to listen carefully to their questions; clear explanations in simple language; an open interaction where they could be honest about what they were actually taking; and the reviewer's honesty about the consequences of taking (or not taking) their medications.[279] Research has also shown that patients can get the most out of their medication review if they know in advance why they are coming, what to expect, and how to prepare. It is therefore advisable to provide patients who are invited for a medication review (or who are eligible for such a review) with education materials about these aspects.[280]

Ideally, the patient interview should reflect a good rapport between patient and professional reviewer, in which the latter does not consider the interview as an opportunity to reinforce instructions around treatment (compliance), but as a space where the expertise of patient and professional are pooled to arrive at mutually agreed goals (concordance).[281;282] It cannot yet be expected that every patient interview turns into such a concordant discussion, if only because this depends on the approach and skills of the individual reviewer. It is important, however, that each interview is concluded with a summary of the agreement with the patient about the treatment and an explanation of what will happen next.[14]

7.2. Non-adherence

Consider the possibility that the patient is taking less of the medication(s) than prescribed

Non-adherence to prescribed drug regimens is a common and important problem. Depending on definition, detection method and user characteristics, non-adherence has been reported to range from 14% to 70%.[283-285] Self-determined drug discontinuance (which could be conceived as the most drastic form of non-adherence) may occur up to 40% of the time.[286] Recent studies indicate that this non-persistence is a major problem for a diversity of drug classes intended for chronic use.[287-291] Among the factors that have been

associated, at one time or another, with non-adherence are the number of medications, the type of drug being taken, prescriptions from more than one doctor, independence when taking medicines, impaired cognitive function, probability of dementia, depression, cost of medications, insurance coverage, and physician-patient communication.[284;285;292-294]

Non-adherence can be either untentional (the patient *cannot* manage his medications) or intentional (the patient *does not want* to manage them as prescribed). In the latter case, the beliefs of the patient (or caregiver) about illness and drug treatment play a crucial role.[295;296] A recent synthesis of qualitative research into the main reasons why people do not take their medications as prescribed identified a number of important lay themes around medication taking.[297] According to this analysis, people evaluate their medications in their own way and encounter difficulties, when weighing up the benefits of taking their medications against the costs of doing so. They place hope in their medications, but a key concern is worries about adverse effects. Another concern is about whether a prescribed regimen fits in with the patient's daily life. People may place more faith in their own observations and/or in alternative sources of information (e.g., peers, books, internet) than in their doctor's advice. They may find it confusing, if objective indicators show improvement while they do not feel any better, or feel worse. They may also find it difficult to assess the long-term impact of preventive medications, which makes some of them uncertain about whether the medication is really necessary (e.g., antihypertensives). Some people have difficulty distinguishing undesirable effects of the medication from the symptoms of their disease. There are also worries about medications that lay testing and evaluation cannot resolve, such as fears about dependence, tolerance and addiction, about masking more serious symptoms, or about the potential harm from taking medications on a long-term basis. Another reason why people may not take their medications as prescribed is that they do not accept their illness and/or regard medications as an unwelcome reminder of that illness. Such people are unlikely to accept their drug treatment as prescribed. For instance, some people with asthma downplay its significance, claiming either that they do not have real asthma or only a slight form. Such patients may leave their preventive medications and only take reliever medications, particularly in social or public situations. For certain drug classes (HIV agents, psychotropic drugs) and in certain age groups (children), people may fear that disclosing their drug use to others will mark them out as being different from their peers, which will lead to stigmatisation or discrimination.[297]

As a result of these considerations and concerns, many people alter the way in which they take their medications, and they may do so without discussing this with their doctors. They may decide not to initiate drug treatment, or to stop taking their medications alltogether. They may also start to self-experiment with their prescribed regimens by taking their medications symptomatically or strategically, or by adjusting doses to minimise unwanted

consequences or to make a regimen more acceptable. Many of these modifications reflect a desire to take as little medications as possible, and sometimes this is also evident from decisions to supplement or replace drug therapies with alternative or non-pharmacological treatments.[297]

An obvious method to assess adherence to drug therapy in daily practice is to look at specific clinical effects (e.g. on cholesterol levels or blood pressure). This is by no means a feasible option for all drug therapies, however, and measurements performed during scheduled patient's visits do not necessarily provide an accurate picture of the intake between visits. Alternatively, it is possible to ask questions to the patient, evaluate prescription refill patterns and/or perform pill counts. All of these methods may help to detect non-adherence to a certain degree, but they are all prone to a risk of overestimating adherence, and their effectiveness varies with the way in which they are executed (e.g., whether or not questions are asked in an open-ended, non-judgmental way).[298-301] A more objective method is direct monitoring of the effects of the treatment (e.g. by measuring blood pressure, cholesterol levels, or peak flow), but this is not a viable option for all types of chronic medications. Another possibility is electronic monitoring of drug intake by providing the medication in a pill bottle with an electronic caps that registers the time of each bottle opening. This approach can not only detect different patterns of nonadherence, but the mere fact that the patient knows that he is being monitored can stimulate him to become more adherent.[302;303] This electronic method is not fool-proof, however, as patients may take out more than one dose at a time or open the bottle without taking the medication.[304] Furthermore, experience with such monitoring electronic devices outside the strict setting of research studies still is rather limited.[305]

General reviews of interventions to improve medication adherence in chronic patients conclude that currently investigated methods are mostly complex, labor-intensive, and not predictably effective and that more studies of innovative approaches are still needed.[306-308] Pending the results of more and better studies, it is important in daily practice to tailor actions for the prevention and reduction of non-adherence as much as possible to the type of non-adherence that is expected or observed: unintentional or intentional. In the latter case, the most important prerequisite is that discussions are based on a good rapport between patient and interviewer (see the previous paragraph). In cases of *unintentional* non-adherence, the following possibilities should also be considered, depending on the specific problem(s) of the individual patient:

1. Educating patients who are not yet sufficiently aware of the necessity to adhere to their prescribed medication regimens
2. Educating patients about practical ways to improve adherence. For instance, it can be rewarding to help patients in selecting cues that will assist them in remembering to take

doses (time of day, meal-time, or other daily rituals). If this is ineffective, the possibility of providing a compliance aid (such as an auditory or visual alarm) may be contemplated.[309]

3. Simplifying prescribed dosage regimens, e.g. once-daily or twice-daily instead of 3 to 4-times-daily[310] and fixed-dose combination products instead of separate products for each drug substance.[311-313]
4. Weekly dispensing in a multi-compartment medication box or other time-specific packing.[314;315] Concrete evidence that this really increases correct use is still meagre,[309;316;317] but it has considerable face validity.

If meaningful, these options can also be combined with each other. In a recent randomized controlled trial in the US, a pharmaceutical care program consisting of standardized medication education, regular follow-up by pharmacists, and the dispensing of medications in time-specific packs increased medication adherence, medication persistence, and clinically meaningful reductions in blood pressure.[318]

Consider the possibility that the patient is taking more of the medication(s) than prescribed

Besides the risk of underuse, the possibility of overuse must be considered for certain drug classes, such as inhaled beta-agoists,[319] benzodiazepines,[320] opioid cough suppressants,[321] laxatives,[322] and triptan derivatives.[323]

7.3. Patient experiences and habits

Consider earlier patient experiences with drugs

Earlier experiences of an individual patient with a particular drug or drug class can be quite relevant, when evaluating the appropriatenes of his use of medications. When a certain drug has been ineffective or toxic in the past, it is important to prevent injudicious reexposure to that particular drug or a closely related one. For example, a previous episode of gastrointestinal bleeding or ulcer is a relevant determinant of NSAID-associated gastrointestinal toxicity.[216;217;324] In other words, when a patient has suffered from an NSAID-related gastrointestinal complication, it is not acceptable to restart this NSAID under the same circumstances.[324;325] Likewise, benzodiazepines should not be restarted in ambulant elderly patients with a history of falls.[40;156]

A recent Dutch study identified elderly drug users in whom drug regimens had been stopped during their hospital stay at a geriatric ward because of adverse reactions. These patients were subsequently followed after their discharge to see whether the stopped drug regimens would be reintroduced outside the hospital. The represcription rate was 27% within the first six months after discharge. Represcription rates were not markedly different for serious or nonserious adverse drug reactions or for adverse drug reactions mentioned or

not mentioned on the discharge letter.[326] It must therefore become easier to exchange and record patient experiences in a standardized way so that they can be systemically taken into account in computerised medication surveillance systems and medication reviews.

Consider special patient characteristics and habits

It can also be relevant to document diverse patient characteristics that may affect drug effects or drug intake, e.g., tobacco smoking,[327] a predilection for natural remedies,[78;328] religious beliefs that stand in the way of using porcine derived drug products,[329] strict adherence to the Ramadan rule of abstaining from any food, beverage, or oral drug from dawn to sunset,[330;331] and so on.

A patient characteristic which particularly deserves more attention than it has received so far is nutritional status, since nutritional deficiencies entail a risk of serious food-drug interactions. Frail elderly people are especially at risk, because they may accrue several risk factors, such as malnutrition, anorexia, alcoholism, chronic disease, and polypharmacy.[133] On the one hand, impairment of nutritional status can have a major impact on the pharmacology of many drugs in the frail elderly, devolving from the physiological alterations it generates. On the other hand, drugs often have, directly and indirectly, a deleterious effect on the nutritional status of the elderly.[332] A list of medications which can be associated with undesired weight loss in older adults has been compiled by Golden et al.[333]

7.4. Dosage forms and packaging

Consider the need of special packaging

It should be recognized that some patients may have difficulty opening foil-wrapped or plastic-wrapped dose units, for instance because they have a rheumatic disorder.[334;335] When a patient seems to be unable to cope with the complexity of his drug-taking regimens, weekly dispensing in a multi-compartment medication box may be contemplated (cf. paragraph 7.2).

Consider whether the patient is able to self-administer dosage forms that require special skills

Many patients find it difficult to split tablets into two equal halves, even if the tablets are provided with a score line.[151;152]

Patients may also lack adequate skills to self-administer certain dosage forms accurately due to age-related or disease-related deficits in cognitive skills, memory or physical dexterity. A good example is the difficulties that elderly patients may have in using their inhaler device correctly.[336] As their perception of their own inhaler skills may not correlate

with actual performance, it is important to ask patients to demonstrate the appropriateness of their inhaler technique.[337] In one study, failure to shake the device, poor coordination of actuation and inhalation and absence of breath holding were the most common errors.[338] In another study, major errors were more common with breath-actuated devices.[337] Unrecognized cognitive impairment or dyspraxia may render elderly patients unable to learn to use an inhaler, and patients with dementia are almost invariably unable to use any form of inhaler.[339] Another concern is that many patients with asthma or COPD are treated with two or three different types of inhalation devices, which may complicate their competence to use each device correctly.[340]

Patients may also experience difficulties with the application of their eye drops, even to the point that self-administered drops may not fall into the conjunctival sac. There are appliances that can help to improve instillation, but care should be taken to select a device that links up with the problem area of the individual user (e.g., alignment or squeezability).[341-343] In addition, it should be checked whether chronic patients continue to use the appliance when their eye drop bottle is replaced by a newly dispensed bottle.[344]

A third potentially worrisome dosage form is the insulin injection.[315] Many elderly patients with diabetes cannot perform self-administration of insulin, because of their poor dexterity, vision or cognitive skills.[345] In addition, users of NPH insulin run a risk that they do not mix this suspension adequately.[346;347]

8. Concluding remarks

We collected various general issues for the implicit screening of medication patterns and grouped them into prescription issues, treatment issues, and patient issues (Table 2). These groups parallel the ongoing development of the pharmaceutical profession from a drug product orientation through drug therapy orientation to drug user orientation.[348]

We provided the general issues with numerous explicit examples and detailed references to other explicit examples, not only to facilitate the education of professional medication reviewers, but also to spark further research into the clinical, humanistic and economic aspects of current drug utilization patterns. We incorporated recent technological developments, such as better linkage between the pharmacy and the laboratory and the increasing range of pharmacogenetic testing possibilities. We also argued, however, that medication reviewers should not restrict themselves to a clinical perspective, but should also side with the patient so that his perspective at drug-related problems is also taken into account adequately. Because at the end of the day, it is the patient who has to cope with his drug therapy, and it is the patient who is in the driver’s seat, when decisions are made whether or not medications are taken as directed.

One final point to be raised here is the need for more studies of medication reviews looking at relevant outcomes. Studies that actually document clinical and humanistic improvements after a medication reviews are still scarce.[1;2;349-352] Some studies have shown favourable trends[9] or significantly positive results,[5;353] but other studies have found no influence on quality of life or rehospitalization,[2;10;354] and even a negative effect on the rate of hospital admissions has been reported.[10] Further well-designed studies are needed to explain such counterintuitive findings, and they should also identify which specific methods of medication review are the most effective and cost-effective.

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Chapter 5

Drug-induced hypoglycaemia in elderly users of antidiabetic agents; incidence and risk factors

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Abstract

Background: More strict control of blood glucose can decrease or delay the onset of microvascular complications of diabetes mellitus. A potential consequence of this more vigorous treatment is an increased risk of hypoglycaemia.

Aim: To study the incidence of and risk factors for hypoglycaemia during antidiabetic drug therapy in an elderly population.

Design and setting: Prospective cohort study in a sample of the Rotterdam Study, a population-based cohort study of 7,983 elderly people.

Method: All users of antidiabetic medicines were followed until they experienced a hypoglycaemic event (hospital admission or blood glucose of 3.5 mmol/ml in GP laboratory testing), died, left the study, or reached the end of the study period. For each treatment group (only oral antidiabetics, only insulin or a combination of oral antidiabetics and insulin) incidence rates of hypoglycaemia were determined.

The influence of the co-factors age, sex, renal function, body mass index (BMI), type of hypoglycaemic agent, polypharmacy, use of selective or non-selective beta-blocking agents, medicines acting on the renin-angiotensin system or medicines influencing CYP2C9 was determined for the total group of users and for users of sulfonylurea derivatives. Subsequently, cofactors with a univariable association were entered into a multivariable model in which a forward selection of significant cofactors was performed.

Results: Hypoglycaemic events are seen in 1 out of 12 patients during the study period. The risk was four times higher in insulin users with or without oral agents (39.1 and 39.0 per 1000 person years) than in users using only oral antidiabetics (9.9 per 1000 person years).

Renal impairment, higher age, polypharmacy, and use of insulin were significantly associated with an increased risk of hypoglycaemia in the total group of antidiabetic users, whereas use of tolbutamide was associated with a decreased risk in this group.

Use of higher numbers of medicines, use of glibenclamide, and use of medicines having an influence on CYP2C9 were associated with an increased risk at hypoglycaemic events for users of sulfonylurea derivatives, whereas tolbutamide appeared to be associated with a decreased risk.

In the multivariable analyses use of insulin and renal impairment remained significant for all users of hypoglycaemic agents. Use of tolbutamide and use of medicines having an influence on CYP2C9 remained significant for users of sulfonylurea derivatives.

Conclusion: Elderly users of antidiabetic medicines are at risk of developing hypoglycaemia. As this risk is greater in insulin users than in users of oral antidiabetic drugs, it seems particularly relevant that elderly insulin users can adequately recognize and rectify upcoming hypoglycaemic events. As the risk of hypoglycaemia is also greater in

elderly users of glibenclamide than in users of tolbutamide, the latter sulfonylurea derivative is the drug of choice in this drug class. Finally, more attention should be paid to interactions between sulfonylurea derivatives and CYP2C9 modifying drugs (such as co-trimoxazole).

Introduction

Diabetes mellitus is a disease in which treatment is shifting. Large trials have shown that more strict control of blood glucose can decrease or delay the onset of micro-vascular complications associated with diabetes mellitus [1,2]. The practice guideline for treatment of type II diabetes mellitus of the Dutch College of General Practitioners starts drug treatment with oral antidiabetics (preferably metformin), when blood glucose levels do not decrease to an acceptable level a combination of oral antidiabetics is prescribed (addition of a sulfonylurea derivative). When blood glucose levels are still too high or when the disease is progressing, insulin is added to the therapy [3-5]. A potential consequence of this more vigorous treatment of diabetes mellitus is an increased occurrence of hypoglycaemic events. Recent studies in the Netherlands and elsewhere have shown that hypoglycaemic events during antidiabetic drug therapy are among the important causes for drug-related hospital admissions [6-8].

In the literature a number of risk factors for hypoglycaemic events have been described, such as age [9-11], recent hospital discharge [9], duration of diabetes [12-14], renal impairment [10], infection [10], polypharmacy [9,14], smoking habits [15], decreased food intake [10,16], drugs interacting with hypoglycaemic agents [10,15-17], and type of hypoglycaemic drug [9,10,14].
Sulfonylurea derivatives are metabolised by CYP2C9 [18-21], and users with a variant genotype may be at increased risk for hypoglycaemia [22]. A recent study has shown that patients who are carriers of a CYP2C9*3 allele require lower doses of tolbutamide to regulate their serum glucose levels than patients with the wild-type genotype [17]. At the same time, medicines inhibiting CYP2C9 can increase the effect of sulfonylurea derivatives [23], probably leading to hypoglycaemia.

Because data from the literature are conflicting, we studied the incidence of and risk factors for hypoglycaemia during antidiabetic drug therapy in a large prospective cohort study of elderly users of hypoglycaemic agents.

Methods

Setting

This study was conducted as a part of the Rotterdam study [24], a prospective population-based cohort study on the occurrence and determinants of disease and disability in elderly people. In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years or over and who had lived in the district for at least 1 year were invited to participate in the study. Of the 10,275 eligible persons 78% participated. Participants gave informed consent and permission to retrieve information from medical and pharmaceutical records. Base-line examination was performed between 1990 and 1993. At baseline, trained interviewers administered an extensive questionnaire during a home

interview covering socio-economic background and medical history, among other topics. During subsequent visits to the study centre, additional interviewing, laboratory assessments, and clinical examinations were performed. Follow-up examinations are carried-out periodically (every 5 years). Data on hospital admissions are obtained by record linkage with Prismant, an organisation which collects admission data from all general and academic hospitals in the Netherlands. For every admission, one discharge diagnosis (mandatory) and up to 9 auxiliary diagnoses (optional) are given based on the ICD9-CM classification [25]. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. Since January 1st, 1997, data from the General Practitioners laboratory, where all laboratory testing for the GPs in the region is performed, have also been linked to the Rotterdam study database.

The medical ethics committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the Rotterdam study.

In the research area there are 7 fully computerised pharmacies linked to one network. During the study, all participants filled 98% of their prescriptions in 1 of these 7 pharmacies. From the moment a participant enters the Rotterdam study data on all drug prescriptions dispensed by automated pharmacies are routinely stored in a database. The data include the date of prescribing, the prescribed daily number of units, Anatomical Therapeutic Chemical Classification (ATC) code [26], and product name.

Cohort definition

For the present study, we enrolled all participants of the Rotterdam Study who were on one or more antidiabetic drugs at the start date of our study period (1 January 1997) as well as incident users who received their first prescription of an antidiabetic after this date. All users were followed from the start date of the study or from the date of their first prescription of an antidiabetic drug during the study period until they experienced a hypoglycaemic event, died, left the study, or reached the end of the study period at 30 June 2005, whichever came first.

Case definition

Patients with a first diagnosis of hypoglycaemia during the study period were defined as cases. Hypoglycaemia was defined as a blood glucose level of 3.5 mmol/ml or less as assessed by the GP's laboratory, or as a hospital admission with the ICD-code 251.0 (hypoglycaemic coma) or 251.2 (hypoglycaemia).The day of the first diagnosis of hypoglycaemia was defined as the index date.

Cofactors

Apart from age and sex, we studied the role of renal function, body mass index (BMI), type of hypoglycaemic agent, and concurrent drugs as potentially important confounders or risk modifiers. Renal function of the included patients was determined by means of serum creatinine levels according to Cockcroft and Gault [27], renal impairment was defined as a creatinine clearance of less than 60 ml/min, including moderate, severe and complete renal failure of the guidelines of the (American) National Kidney foundation (K/DOQI) [28,29]. Body mass index (BMI, weight of a person related to the square length of this person) was categorised as BMI$\leq$ 25 versus BMI> 25.

Drug use was defined as current if the index date fell within the prescription length of that drug. Hereto, the prescription length of each drug was calculated as the number of filled tablets/capsules divided by the prescribed daily number. Because the following drugs are associated with an increased risk at hypoglycaemia, we recorded whether they were used in the period of 90 days before the index-date: selective or non-selective beta-blocking agents [30,31], medicines acting on the renin-angiotensin system (ACE-inhibitors or AII-antagonists) [32,33]. Because for some of the medicines an increased risk has been observed at the start of therapy, we distinguished between starters (<30 days current use), recently started users (30-90 days current use) and long-term users (> 90 days current use). The number of prescriptions for any drug in the period of 90 days before the index date was recorded. For each index date, this was categorised by patients having less than 10 prescriptions and patients having 10 or more prescriptions dispensed in the period of 90 days before the index date.

Because sulfonylurea derivatives are metabolised by CYP2C9 [18,20,21] we studied the effect of CYP2C9 genotype of the study participants, in which individuals with genotypes CYP2C9/2*3 and CYP2C9/3*3 were categorised as slow metabolisers [19].

To study the specific effects of medicines influencing CYP2C9, we also studied the use of CYP2C9 inhibitors and other substrates for CYP2C9 [23] in the period of 90 days before the index-date: nateglinide (A10BX03), rosiglitazone (A10BG02), amiodarone (C01BD01), losartan (C09CA01), irbesartan (C09CA04), fluvastatin (C10AA04), co-trimoxazole (J01EE), fluconazole (J02AC01), voriconazole (J02AC03), isoniazid (J04AC01), tamoxifen (L02BA01), phenylbutazone (M01AA01), diclofenac (M01AB05), piroxicam (M01AC01), meloxicam (M01AC06), ibuprofen (M01AE01), naproxen (M01AE02), celecoxib (M01AH01), probenicid (M04AB01), phenytoine (N03AB02), amitriptyline (N06AA09), fluvoxamin (N06AB08), sertraline (N06AB06) and fluoxetine (N06AB03). Analyses were performed for use of the individual drugs in this group and for use of any medicine influencing CYP2C9 in the period of 90 days before the index date.

Statistical analysis

The incidence rate of hypoglycaemic events was determined separately for subjects using only oral antidiabetics, for users of insulin alone, and those who were using both on the index date. The incidence rate was calculated by dividing the number of hypoglycaemic events in the particular treatment group during follow-up by the cumulative amount of person years treatment in the particular groups on the index date. Incidence rates were converted as numbers per 1000 person years treatment. We calculated the hazard ratio (95% confidence intervals) of each cofactor as described above, both for the total group of users and for users of sulfonylurea derivatives, in a Cox proportional hazards model (SPSS 12.0 software ltd). In our analyses calendar time in days was used as the time axis.

For all cofactors we studied whether there was a univariable association with hypoglycaemia in an age- and sex-adjusted model. Risk factors that were based on 3 exposed cases or less were discarded as being insufficiently reliable. Effect modification was studied with interaction terms in a multivariable model. If statistically significant, analyses were stratified on the effect modifier. Subsequently, cofactors with a univariable association were entered into a multivariable model in which a forward selection of significant cofactors was performed (p=0.05).

Results

Study population at baseline

In the database 784 users of antidiabetics could be identified. Their mean age was almost 74 years and 59.7 per cent of the patients were women. About 22 per cent of this population was suffering from renal impairment, and about 80 per cent of the population had a body mass index of 25 or more.

There were 447 individuals with the wild type (*1/*1) of CYP2C9 (66.9%). The remainder had either one or two *2 or *3 variant alleles. Twelve patients (1,8%) were identified as slow metabolisers for CYP2C9 having the CYP2C9 genotypes *3/*3 or *2/*3.

At baseline almost 83 per cent of the included subjects was treated with oral antidiabetics only, 13.5 % of the population was treated with insulin only and almost four per cent of the population was treated with a combination of insulin and oral hypoglycaemic agents (Table 1).

For 66 of the 784 included subjects, a hypoglycaemic event was registered during the study period (8.4%). Ten of these subjects were admitted to a hospital because of hypoglycaemia, the remaining 56 cases had a blood glucose level of 3.5 mmol/ml or less during GP laboratory testing.

Table 1. Characteristics of the study population at baseline

Variable	Number of patients (%)
Age at base-line (mean ± SD) in years	73.82 (7.84)
Female gender	468 (59.69)
Body mass index (mean + SD) in kg/m^2 (n=710)	28.24 (3.93)
Body mass index < 25 in kg/m^2 (n=710)	136 (19.2)
Renal impairment (creatinine clearance < 60 ml/min) (n=533)	117 (21.95)
> 10 prescriptions dispensed in 90 days before baseline	108 (13.78)
CYP2C9 2*3 or 3*3 genotypes (slow metabolisers) (n=668)	12 (1.80)
Any use of any medicine influencing CYP2C9 during study period	425 (54.21)
Any use of tolbutamide during study period	255 (32.53)
Any use of glibenclamide during study period	173 (22.07)
Any use of glimepiride during study period	165 (21.05)
Any use of gliclazide during study period	80 (10.20)
Antidiabetic use	
- Only oral antidiabetics	647 (82.53)
- Using insulin	106 (13.52)
- Using insulin and oral antidiabetics	31 (3.95)

Table 2 shows that the highest incidences of hypoglycaemia occurred in the groups of patients using insulin with or without oral hypoglycaemic agents (39.1 and 39.0 per 1000 person years, respectively). The incidence for subjects using only oral antidiabetics was about one fourth of that of insulin users (9.9 per 1000 person years), a statistically significant difference (HR 3.9 [95%CI: 2.3-6.6]).

Table 2. Incidence of hypoglycaemia for all users of antidiabetics and for the subgroups

	Person years of treatment	Total number hypoglycaemic events (cases)	Incidence (per 1000 person years)	95% confidence interval
Total group	3729.2	66	17.7	13.8-22.3
Using only oral antidiabetics	2730.7	27	9.9	6.6-14.2
Using insulin	768.4	30	39.0	26.9-55.0
Both insulin and oral antidiabetics	230.1	9	39.1	19.3-71.4

Influence of cofactors

Table 3 shows an increased incidence of hypoglycaemic events in antidiabetic users with higher age, renal impairment, polypharmacy and use of insulin. In contrast, the use of tolbutamide was associated with a decreased risk of hypglycaemia (OR_{adj} 0.16; CI95% 0.04-0.66). Significant effects were seen for use of use of amitriptyline and sertraline, because of the low number of cases (3 cases and 1 case respectively) these cofactors were discarded as being insufficiently reliable.

Table 3 Factors associated with the risk at hypoglycaemic events for the total group of users of antidiabetics. All co-factors (see methods) were tested, only results with significant results and with a sufficient number of cases were included in the table

Risk factor	No. of cases	Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI)
Age 75 years or over			
- No	15	Reference	n.a.
- Yes	51	1.952 (1.096-3.477)	
Renal impairment (n=533)			
- no	28	reference	Reference
- yes	15	1.964 (1.045-3.689)	2.005 (1.008-3.989)
$\geq$ 10 prescriptions dispensed in period 90 days before index date			
- No	46	Reference	Reference
- Yes	20	2.195 (1.297-3.716)	2.129 (1.257-3.606)
Use of insulin			
- No	27	Reference	Reference
- Yes	39	2.504 (1.527-4.105)	3.083 (1.846-5.148)
Use of tolbutamide			
- No	64	Reference	Reference
- Yes	2	0.169 (0.0410.692)	0.160 (0.039-0.657)

* sex and age adjusted

Factors that were significantly associated with hypoglycaemia in users of sulfonylurea derivatives are presented in Table 4. Renal impairment, which was associated with hypoglycaemia in all users of antidiabetics did no longer show a significant association in users of sulfonylurea derivatives. On the other hand, having 10 or more prescription in the period of 90 days before the index date was also associated with an increased risk of hypoglycaemia in these users. Use of glibenclamide, a long acting sulfonylurea derivative, appeared to increase the risk of hypoglycaemic events, as did the use of medicines having an influence on CYP2C9. On the contrary, use of tolbutamide appeared to be associated with a decreased risk at hypoglycaemia. Significant effect modification was seen for use of glibenclamide and use of medicines having an influence on CYP2C9, so odds ratios were adjusted for this interaction effect.

Significant effects were seen for use of cotrimoxazole (2 cases), amitrityline (2 cases), sertraline (1 case) and recent start (< 30 days current use) of ace-inhibitors (3 cases), because of the low number of cases these cofactors were discarded as being insufficiently reliable.

Table 4 Factors associated with the risk of hypoglycaemic events in sulfonylurea derivative users. All co-factors (see methods) were tested, only associations with significant and a sufficient number of cases were included in the table.

Risk factor	No. of cases	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
≥ 10 prescriptions in period 90 days before index date			
- No	19	Reference	Reference
- Yes	10	2.250 (1.089-5.072)	2.315 (1.055-5.079)
Use of tolbutamide			
- No	27	Reference	Reference
- Yes	2	0.153 (0.037-0.650)	0.148 (0.035-0.625)
Use of glibenclamid			
- No	11	Reference	Reference
- Yes	18	2.434 (1.141-5.192)	2.347 (1.093-5.041)
Use of medicines having an influence on CYP2C9			
- No	19	Reference	Reference
- Yes [b]	10	2.790 (1.294-6.015)	2.662 (1.230-5.759)

[a] sex and age adjusted

b medicines having an influence on CYP2C9; cotrimoxazole two cases, ibuprofen two cases, amitriptylin two cases, rosiglitazone one case, sertralin one case, losartan one case, amiodarone one case

Table 5 shows the factors that remained significant in multivariable analyses. For all users of antidiabetics use of insulin and renal impairment remained significant in the multivariate model, both factors leading to an more than two-fold increase in the risk at hypoglycaemic events. For users of sulfonylurea derivatives use of tolbutamide and use of medicines having an influence on CYP2C9 both remained significant. Tolbutamide gave a decreased risk at hypoglycaemic events whereas use of medicines having an influence on CYP2C9 increased this risk.

Table 5 Factors associated with risk at hypoglycaemic events at multivariate level. All cofactors that were significant in univariable analyses were included in the analyses, selection of cofactors was performed in a forward and backward procedure

Risk factor	All users of antidiabetics		Users of sulfonylurea derivatives	
	No. of cases	Odds Ratio (95% CI)	No. of cases	Odds Ratio (95% CI)
Renal impairment (n=533)				
- no	28	reference	-	-
- yes	15	2.090 (1.112-3.931)		
Use of insulin				
- No	19	Reference	-	-
- Yes	24	2.438 (1.329-4.474)		
Use of tolbutamide				
- No	-	-	27	Reference
- Yes			2	0.155 (0.037-0.653)
Use of medicines having an influence on CYP2C9	-	-		
- No			19	Reference
- Yes			10	2.774 (1.286-5.986)

Discussion

Summary of main results

The current study shows that hypoglycaemic events can be seen in a relatively high proportion of patients treated with antidiabetics, namely in 1 out of 12 users of antidiabetics, with an incidence of 17.7 per 1000 person years (table 2). The risk was four times higher in insulin users, with or without oral agents (39.1 and 39.0 per 1000 person years) than in users using only oral antidiabetics (9.9 per 1000 person years).

Of the risk factors that were associated with an increased risk of hypoglycaemia in the univariable analyses, use of insulin and renal impairment remained significant in the multivariable analyses for all users of hypoglycaemic agents. For users of sulfonylurea derivatives the increased risk associated with the use of medicines having an influence on CYP2C9 remained significant. In contrast, tolbutamide remained associated with an decreased risk of hypoglycaemia.

Comparison with literature

The incidence of hypoglycaemic events has been studied before by others. In a study by van Staa et al. in which a first diagnosis of hypoglycaemia in a GP database was the endpoint, a higher incidence was found for users of sulfonylurea derivatives (17.77 per 1000 person years). Subjects using insulin as co-medication were also included in this group of patients, which may explain that the incidence of hypogylcaemia was higher than that in our study [34].

In a study by Stahl et al. a much lower incidence was found (0.92 per 1000 person years) for users of sulfonylurea derivatives. In this study, however, only cases of severe hypoglycaemia leading to hospital admissions had been included [16].

A study performed by Shorr et al. observed incidence rates comparable to the ones we found (12.3 for sulfonylurea-users, 27.6 for insulin users and 33.8 for users of both sulfonylurea derivatives and insulin)[9,35]. However, this study also used serious hypoglycaemia (defined by hospitalization, emergency department admission, or death associated with hypoglycaemic symptoms) as endpoint.

Like us, others have found that higher age[9-11] and renal impairment[10] are associated with an increased risk at hypoglycaemic events. However, in our analyses renal impairment no longer had a significant effect when we looked specifically at users of sulfonylurea derivatives.

We confirmed previous findings that the use of higher numbers of medicines is a risk factor [9,14]. When we specifically looked at use of medicines influencing CYP2C9 by users of sulfonylurea derivatives, we also saw an increased risk at hypoglycaemia. This was also found by others, Juurlink found that elderly patients using glibenclamide who were

admitted with a diagnosis of hypoglycemia were more than 6 times as likely to have been treated with co-trimoxazole in the previous week (adjusted odds ratio, 6.6; 95% confidence interval, 4.5-9.7) [36]. An increased risk of hypoglycaemia in users of sulfonylurea derivatives taking sulfonylurea-potentiating drugs has also been observed in other studies [14,34].

We confirmed that hypoglycaemia is more common in patients using glibenclamide than in patients using shorter acting sulfonylurea derivatives [14,16,35,37-39]. This increased risk for glibenclamide is caused by its metabolites which have blood glucose lowering properties and have long half-life times [37-39].

Twelve subjects (1.8%) in our study were identified as slow metabolizers for CYP2C9. This percentage falls in the range of 1-3% poor CYP2C9 metabolizers that has been found for Caucasian populations in previous studies [22,23]. In the present study we could not identify an increased risk of hypoglycaemia for CYP2C9 poor metabolizers. Possibly, this was caused by the rather small group of subjects in combination with the fact that genotyping was not performed for all subjects included in the study. In contrast, another study with an even smaller number of cases found a significant association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia [22]. In this latter study two of the twenty cases (10%) had a CYP2C9 poor metabolizer genotype and five cases (25%) were treated with CYP2C9 inhibiting medicines. So more research on the potential effects of CYP2C9 poor metabolizer genotype and CYP2C9 inhibiting medicines is warranted.

Limitations of the study

Although we tried to perform our study as reliably as possible there were some limitations to our study. Firstly, not all variables included in our analyses were completed for all subjects (e.g. CYP2C9 genotyping and renal impairment), these missing values may have influenced the results of our analyses.

Secondly the number of cases and included patients were rather small. For some cofactors we saw an association, but because of the small number of cases (1-2) and the low frequency of some of the cofactors (e.g. use of particular medicines, CYP2C9 slow metabolisers) we could not state with certainty that there actually was an association. These analyses should be repeated in databases containing larger numbers of diabetic patients, using all kinds of medicines.

Furthermore, patient characteristics were copied to our database as they had been recorded in the Rotterdam study database. These patient characteristics may not have been updated systematically during the study period. Yet some of these patient characteristics do not necessarily remain constant over a larger period of time (e.g. renal function, BMI etc).

Finally, we did not focus our analyses on hospital admissions related to hypoglycaemia but also included milder cases (blood glucose values measured in the general practitioners laboratory of $\leq$ 3.5 mmol/ml). Subjects with low blood glucose levels as measured at the general practitioners laboratory may not have acute complaints, but they may be at increased risk of more serious hypoglycaemic events. In addition, GPs will use portable blood glucose measuring equipments in acute situations, these values were not included in our study. Furthermore, our study did not take in that more experienced diabetic patients may selfadminister a source of glucose to cope with an upcoming hypoglycaemic event. Hence, the incidence of hypoglycaemic events as determined in our study is probably an underestimation of the total number of hypoglycaemic events in the study population. Because these effects concern the whole population of diabetic patients, it is unlikely that they have had a large influence on the estimates as determined in our study.

Recommendations for daily practice and further research

Recent developments aim at more strict control of blood glucose levels and insulin treatment in type II diabetes is started easier than a few years ago. We have confirmed that elderly users of insulin are at increased risk of hypoglycaemic events. Consequently it seems important that these users can adequately recognize and rectify upcoming hypoglycaemic events. In the Netherlands, this aspect could be a focus of attention for the practice nurses that are nowadays guiding most elderly patients who are starting insulin treatment.

Renal impairment was associated with an increased risk of hypoglycaemic events, although this increased risk lost its significance when we looked specifically at the group of sulfonylurea derivative users. For patients with renal impairment lower insulin dosages are needed in comparison with patients with a normal renal function [40]. In the elderly, in general, renal function is diminishing. The average glomerular filtration rate in the elderly is declining with age, with a large interindividual variability [41]. Furthermore, diabetic patients are at risk of developing nephropathy which may further decrease their renal function [42].

In our study we saw an increased risk at hypoglycaemic events for users of glibenclamide (18 cases based on a total of 173 glibenclamide users 10.4%), whereas for tolbutamide a much lower risk of hypoglycaemia was observed (2 cases based on a total of 255 tolbutamide users, 0.78%). Although most guidelines and handbooks mention this risk, glibenclamide still was frequently used in our (elderly) study population. Because of the lower risk for hypoglycaemia, tolbutamide remains the drug of choice when elderly have to be treated with sulfonylurea derivatives.

About a third of all cases in the users of sulfonylurea derivatives appeared to be associated with drug drug interactions at the CYP2C9 level. The interaction between sulfonylurea derivatives and co-trimoxazole (especially tolbutamide) is routinely monitored by only one of the three main medication surveillance systems in Dutch community pharmacies. They state the interaction is caused by a combination of CYP2C9 inhibition and protein displacement. This system advises to dispense an alternative antibioticum if possible, but also allows the dispensing of co-trimoxazole provided extra precautions are taken. (e.g. inform the patient about symptoms and treatment of hypoglycaemia)[43]. In our study 31 patients were concomitantly using sulfonylurea derivatives and co-trimoxazole, of which two were suffering from hypoglycaemia.

We also found evidence to suggest that sulfonylurea derivatives may interact with other drugs than co-trimoxazole having an influence on CYP2C9 (ibuprofen, amitriptylin, rosiglitazone, sertralin, losartan and amiodarone). These other interactions are not yet routinely monitored by Dutch medication surveillance systems, so more research in this field is warranted.

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Chapter 6

Treatment reviews of older people on polypharmacy in primary care: cluster controlled trial comparing two approaches

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Abstract

Background: Older people are prone to problems related to use of medicines. As they tend to use many different medicines, monitoring pharmacotherapy for older people in primary care is important.

Aim: To determine which procedure for treatment reviews (case conferences versus written feedback) results in more medication changes, measured at different moments in time. To determine the costs and savings related to such an intervention.

Designof study: Randomised, controlled trial, randomisation at the level of the community pharmacy.

Setting: Primary care; treatment reviews were performed by 28 pharmacists and 77 general practitioners (GPs) concerning 738 older people (≥75 years) on polypharmacy (≥ 5 medicines).

Methods: In one group, pharmacists and GPs performed case conferences on prescription-related problems; in the other group, pharmacists provided results of a treatment review to GPs as written feedback. Number of medication changes was counted following clinically-relevant recommendations. Costs and savings associated with the intervention at various times were calculated.

Results: In the case-conferences group significantly more medication changes were initiated (42 vs 22, $p = 0.02$). This difference was also present 6 months after treatment reviews (36 vs 19 $p = 0.02$). Nine months after treatment reviews, the difference was no longer significant (33 vs 19 $p = 0.07$). Additional costs in the case-conferences group seem to be covered by the slightly greater savings in this group.

Conclusions: Performing treatment reviews with case conferences leads to greater uptake of clinically-relevant recommendations. Extra costs seem to be covered by related savings. The effect of the intervention declines over time, so performing treatment reviews for older people should be integrated in the routine collaboration between GPs and pharmacists.

Introduction

Many older people suffer from chronic diseases for which medicines should be used. Older patients are more prone to problems related to their medicines because of the higher number they use, and because of a decline in cognitive and physical functioning. A previous study found that two-thirds of all older people have problems using their medicines correctly; and that these problems could lead to a deterioration in clinical condition for one of four older patients[1]. Another study by the current authors found that there are prescription-related points of concern, possibly leading to a deterioration in clinical condition, in the pharmacotherapy of almost all older patients studied; for example, using diazepam, a benzodiazepine with a long half-life and hence unsuitable for use by older people. These problems were considered to be of direct clinical relevance in 30% of patients[2]. Th current intervention study focuses on prescribing medicines for older patients, rather than on user-related problems.

Monitoring pharmacotherapy for older people in primary care is important. One possible approach is the use of treatment reviews for individual patients by trained professionals (for example general practitioners (GPs), clinical or community pharmacists, or two healthcare professionals of different professional backgrounds together). While earlier studies have shown that treatment reviews can be useful[3-6], supplementary studies are still needed to evaluate the comparative effectiveness of various models for treatment reviews[7].

This study compared two procedures for treatment review by a team consisting of a community pharmacist and a GP. In one group (termed the case-conference group) the pharmacist and GP personally discussed problems, as identified in the pharmacotherapy of the patient through academic detailing or case conferences, and drew up a pharmaceutical care plan for each patient. In the other group (termed the written-feedback group) the pharmacist passes the results of a treatment review to the GP as written feedback. The former procedure may produce more and better results, but also could be more time consuming and costly, and require more organisational activity.

Effects and cost differences were determined at 6 and 9 months after the intervention. Furthermore, yearly savings in medicine costs for each year the medication change persisted were determined. The investigators were particularly interested in the medication changes made in response to clinically-relevant recommendations made by the pharmacist to the GP.

Method

Study design

The study was a clustered, randomised, controlled trial. Pharmacists in both intervention arms conducted treatment reviews. Written feedback only was given to the GPs in one

group. In the other group, the pharmacist and the GP had personal contact in a case conference in which a pharmaceutical care plan was drawn up for each patient. Treatment reviews were performed between March and May 2004.

Randomisation across the intervention arms was at the level of the community pharmacy. Each pharmacy included GPs in only one of the intervention groups, so that contamination of the effect was prevented.

The unit of analysis was the GP (who prescribed the medicines that were evaluated in the treatment review). Patients were considered to be nested within general practices. On the basis of a power calculation using an intra-cluster correlation coefficient of 0.03 (deduced from the researchers' in-depth analysis of polypharmacy for older people[2]), and with the aim to detect a difference of 10% in medication changes following the recommendations between the groups [8], an estimated sample of at least 20 pharmacies, each associated with 3 GPs with 10 participating patients for each GP, was required.

Study population: participating healthcare professionals and their patients)

In this intervention study, Service Apotheek Nederland, a franchise organisation supporting independent community pharmacies in their professional activities, supported this research with their organisational skills. All pharmacies registered with Service Apotheek Nederland (N = 120) were invited to participate in the study. Participating pharmacies each contacted three GPs (convenience sample). Ten home-dwelling older people (aged ≥ 75 years), registered by one GP, who were using at least five prescription medicines continuously at the start of the study were selected at random from a large database in which community pharmacy dispensing data are collected.

Pharmacy codes for these patients were presented on a secure web page that was only accessible to the participating pharmacist. The pharmacist had to exclude older patients who were terminally ill, deceased, lived in a home for older people, younger than 75 years, or used fewer than five medicines continuously; this could be done online. If patients were excluded, new patients were presented on the web page as long as these patients met the criteria.

Computerised screening tool for detecting suboptimal prescribing for older people

The Foundation for Pharmaceutical Statistics (SFK) collects pharmacy dispensing data from 90% of the community pharmacies in the Netherlands. The SFK gathers these data in an anonymous format: only patient codes are recorded to safeguard the privacy of patients. This allows the SFK to reconstruct utilisation patterns of individual patients without any danger of exposing the patients identities[9].

A computerised screening tool was designed to search the SFK records for suboptimal prescribing for older people. This computerised screening tool was an aid for participating pharmacists: they could obtain the results of these searches (as performed in January 2004) on a secured website. Because the pharmacists have to send dispensing files from the pharmacy system to the SFK database at the end of a month, the SFK always has a delay in the database. The searches were performed in the database including the data of January 2004. Searches were not updated during the study period. Pharmacists received a graphical representation of the pharmacy record of each participant and a list of potential problems identified by the computerised screening tool. This information lists the Anatomical Therapeutic Chemical code[10] of the medicine(s) causing the problem, a description of the problem, and some directions for potential improvement.

Intervention

All participating pharmacists were invited to attend a training session dealing with problems related to medication use in older people and treatment reviews. After this training session, pharmacists were randomised and the pharmacists in both intervention groups performed treatment reviews with the support of the computerised screening tool. They had to decide which of the recommendations highlighted by the computerised screening tool should be given to the GP, and whether additional recommendations concerning the pharmacotherapy of these patients should be highlighted.

The two intervention groups differed in their organisational models (Figure1):

- *Written-feedback group:* pharmacists listed all recommendations per patient and delivered them to the GP's office. The pharmacist did not follow up cases.
- *Case-conferences group:* the pharmacist and GP discussed all recommendations with each other, including other concerns about the patients (if any). The pharmacist and the GP together filled in a standardised pharmaceutical care plan, in which they addressed who was responsible for the activities in this plan. Three months later the pharmacist checked whether these activities had been carried out.

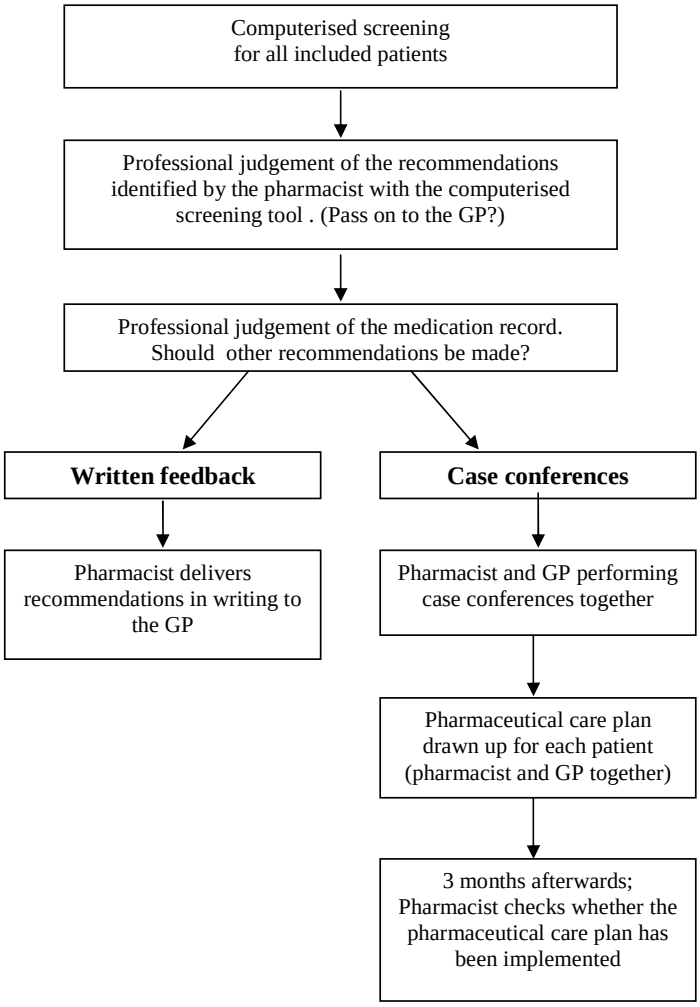
Variables and instruments

Medication changes following clinically-relevant recommendations

Researchers determined how many clinically-relevant recommendations were made by the pharmacist; and determined the number of medication changes consistent with these recommendations that could be detected in the medication records. To verify that differences in the number of medication changes were not caused by variation in the number of recommendations made, a secondary outcome measure was used that relates the

number of recommendations followed to the number of recommendations made: the percentage of clinically relevant recommendations leading to medication changes.

Figure 1. Flow diagram of the intervention study comparing two procedures for medication reviews of older people on polypharmacy in primary care



A copy of the list of recommendations that the pharmacist made for each patient was sent to the research team. Six and 9 months after treatment reviews, pharmacy records and drug-dispensing profiles (graphical representations of the pharmacy records) were received by the research team from the pharmacies. Two experienced pharmacy assistants determined whether the recommendations had led to medication changes, whether these

medication changes had been maintained, and whether results of the recommendations as proposed could be identified in drug-use profiles and pharmacy records (for example, is the drug used for the right indication? Is blood pressure checked regularly?). If the researchers could not determine whether action had been taken in response to a recommendation was considered to have not been acted on.

After 9 months, researchers recorded whether medication changes that were present at 6 months had been maintained. It could not be assumed that medication changes initiated more than 6 months after the treatment reviews were caused by the intervention, so these medication changes were not included.

Clinical relevance of recommendations by pharmacists

Clinical relevance was assessed for all recommendations (as they were identified by the computerised screening tool or by pharmacists) that were communicated to GPs. Recommendations were classified as:

- Clinically relevant: recommendation will lead to improvement in the general health of the patient.
- Potentially relevant: for example, relevance depending,on the medical condition of the individual patient.
- Clinically irrelevant: recommendation will not lead to improvement in the general health of the patient.

For most of the recommendations identified by the computerised screening tool, clinical relevance was based on an earlier in-depth analysis of pharmacotherapy[2], while for some of the remaining problems it was based on the literature[11,12]. For the recommendations that the pharmacists identified themselves, clinical relevance was based on the previous in-depth analysis[2] or was determined by an expert panel during the present study.

The expert panel consisted of a GP, a community pharmacist, a geriatrician, and a clinical pharmacist who were chosen because of their experience in geriatric pharmacology. The expert panel did not include individual members of the participating pharmacies or general practices. Clinical relevance was determined using a consensus method. Panel member had to fill in their individual opinions regarding the clinical relevance of each recommendation. Panel members received overviews in which their own scores were compared with those of the other panel members. During a consensus meeting on the telephone, panel members discussed all differences until they reached consensus about the clinical relevance of each particular recommendation.

Changes in costs of medicines used

For each medication change, the difference in medication costs at 6 and 9 months after the treatment review was determined. Researchers determined the differences in medication costs if the medication changes, persisting until 9 months after the intervention, would persist for another 12 months. Differences in medicine costs were determined by adding the costs of the medicines and the dispensing fees for the pharmacy following legal regulations (15-days prescriptions for all new medicines, followed by 3-month prescriptions for all medicines, except hypnotics for which the legal maximum prescription period is 30 days). Supplemental costs caused by wastage were not included in the calculations.

Time consumed by this intervention

Participating healthcare professionals were asked to keep a separate time log of all intervention activities for each patient. This time log was used to calculate the costs of the treatment reviews (at an assumed rate of 50 euros per hour for each healthcare professional, analogous to another study in the Netherlands[13]).

No reimbursement was given for participation in the study. Participating pharmacists were invited to a training session in which medication-related problems and the process of treatment reviews concerning older people were dealt with. Pharmacists were offered free use of the computerised screening tool.

Data analysis

Baseline characteristics of the participating healthcare professionals and participants in both intervention groups were compared using X^2 tests for dichotomous values and Student's t-tests for differences in means of numerous values.

The type of problem, directions for improvement, origin (computerised screening tool or pharmacist) and clinical relevance for each recommendation passed on to the GP were entered into a Microsoft® Access database. Whether recommendations were acted on, partially acted on, or not acted on at all at the various times of measurement, was also recorded in this database. Actual changes in costs associated with the interventions were also recorded in this database. The database was analysed using SPSS (version 12.0).

Because patients in this study were nested within general practices, researchers analysed the number of medication changes following clinically-relevant recommendations at the level of GP. For each GP the total number of recommendations acted on was determined. Because the number of recommendations followed by the different GPs was not normally distributed, differences between groups were determined using X^2 statistics at this level. Before X^2 statistics could be performed, the number of recommendations followed was

categorised (zero, one or more than one recommendation followed). Multilevel (mixed model) analysis was performed to determine whether differences in costs and in percentages of recommendations followed were present. A model with a random intercept and all other variables fixed was used. Multilevel analyses were performed using SAS (version 8.2)[14] .

Results

Study population

Of the 120 pharmacies invited, 29 (with 84 accompanying GPs; three pharmacies could only find two GPs to take part in the study) were included in the randomisation. Four GPs were subsequently excluded for different reasons. During the intervention period, one pharmacy in the written-feedback group dropped out (along with three accompanying GPs) because they could not find the time to deliver the pharmacy dispensing data of patients to the research team.

Data for 28 pharmacies were gathered and added to the database (13 written feedback and 15 case conferences) accompanied by data for 77 GPs. A total of 738 patients were included (351 in the written-feedback group and 387 in the case-conference group).

Before the 6-month assessments, but after the treatment review, 37 patients were excluded for various reasons (Figure 2). In the period between 6 and 9 months, 16 participants were excluded.

Figure 2. Inclusion and exclusion of participants and patients in RCT comparing two procedures for medication reviews concerning home-dwelling elderly people on polypharmacy in primary care

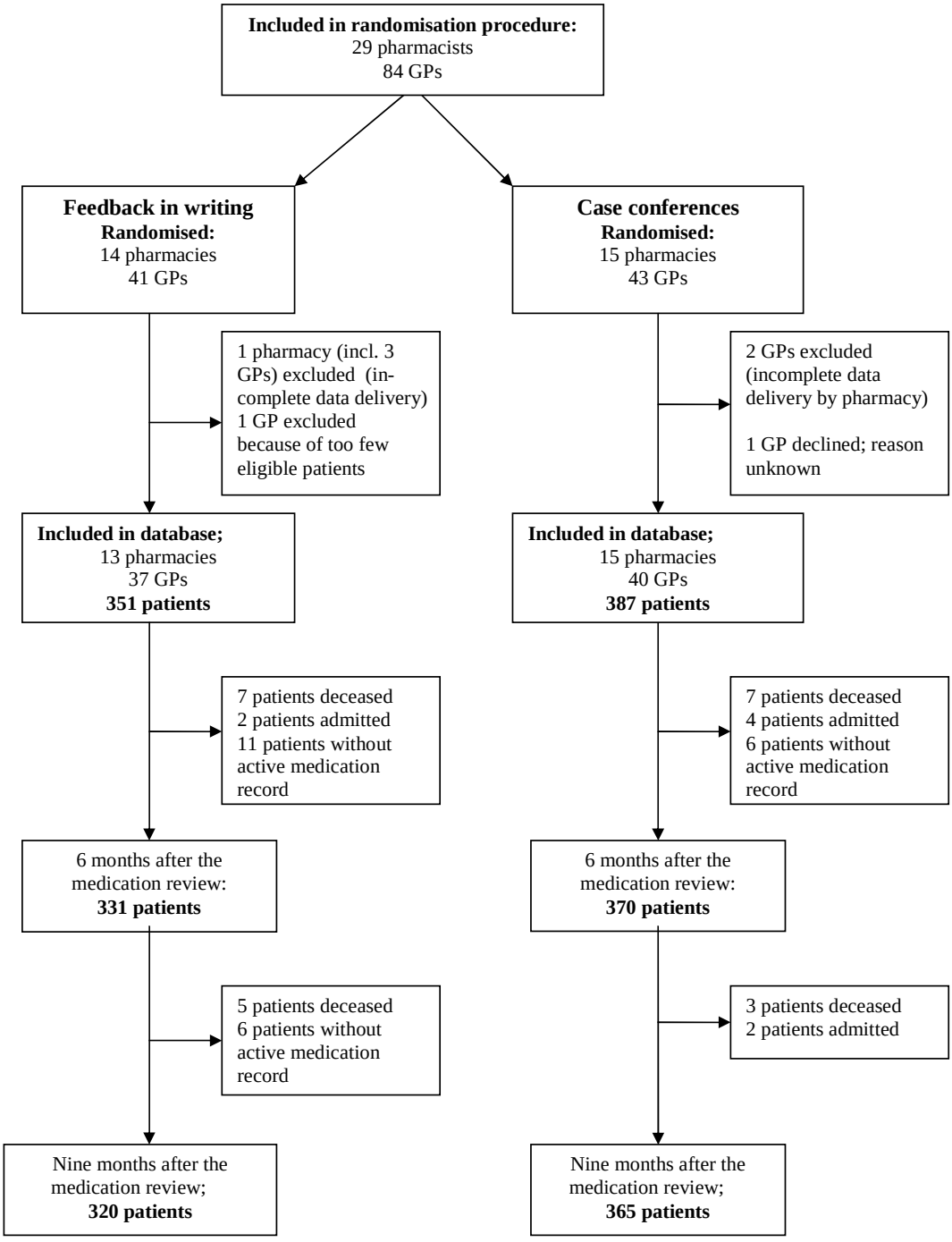


Table 1 shows the characteristics of the participating pharmacists, GPs, and their patients. The patient and pharmacy characteristics for the written-feedback group and the case-conference group were comparable. Of the GP characteristics, only the number of single-handed practices was unevenly distributed among intervention groups.

Table 1. Characteristics of participating patients, GPs, and pharmacies (Student t-test for differences in continuous values and Chi-square statistics for binominal values)

Characteristics	Feedback in writing	Case conferences
Pharmacies	13	15
Pharmacists employed in the pharmacy	2.0	1.9
Percentage of elderly patients (≥75 years) at the pharmacy	8.9 %	13.4 %
Percentage of pharmacies with 350 or more prescriptions a day[1]	58.3 %	71.4 %
General practitioners	37[2]	40[3]
Percentage of single-handed practices	59.3	32.4 *
Number of patients in practice[4]	3168	3279
Percentage of patients 75 years or older in general practice	10.6 %	13.5 %
Patients	351	387
Age of patients (in years)	81	81
Percentage of men	34.9 %	40.6 %
Average number of medicines used by participants (as measured by the computerised screening tool)	7.3	7.1

* p=<0.05

[1] Two pharmacists did not answer the question about the daily number of prescriptions, evenly divided over both intervention groups

[2] We received 27 questionnaires from GPs in the written feedback group (73% response)

[3] We received 37 questionnaires from GPs in the oral feedback group (93% response)

[4] Seven GP's did not answer the question about the number of patients in practice, three in the feedback in writing group, four in the group with case conferences

Number and clinical relevance of recommendations as presented to GPs

Participating pharmacists made a total of 1569 recommendations regarding the pharmacotherapy of 624 participating patients; no recommendation was given for 114 (15.4%) patients. The computerised screening tool identified 62.0% of the recommendations that were passed on to the GPs; the pharmacists themselves identified 38%. Pharmacists in the case-conference group identified significantly more recommendations themselves than the pharmacists in the written-feedback group (41.7% versus 34.2%, $p = 0.003$).

Table 2 shows the number and types of recommendations presented to GPs. The recommendations were categorised by clinical relevance. Some recommendations with limited clinical relevance were made (3.4%); for example, prolonged use of vitamin preparations without an indication. Many recommendations with potential clinical relevance were made (77.3%); for example, performance of regular checks. Most clinically relevant recommendations were about prescribing the correct geriatric dosage (104 recommendations), followed by prescribing medicines considered unsuitable for use by older people (99 recommendations), and prescribing omissions (34 recommendations).

The mean number of recommendation per patient made by the pharmacists in the case-conference group seemed to be higher than that in the group with written feedback; however, this difference was not statistically significant (p=0.059).

Table 2. Numbers, types, and clinical relevance of medication recommendations from the pharmacist to the GPs

Type of recommendation	Feedback in writing (percentage within category of clinical relevance)			Case conferences (percentage within category of clinical relevance)			Example of clinically relevant recommendation
	Not clinically relevant	Potentially clinically relevant	Clinically relevant	Not clinically relevant	Potentially clinically relevant	Clinically relevant	
Dose unsuitable for 75+	1 (4.8)	51 (9.5)	62 (42.2)	0	73 (10.8)	42 (26.9)	Use of more than 20 mg of temazepam daily
Medicines not suitable for 75+	2 (9.5)	18 (3.3)	35 (23.8)	0	14 (2.1)	64 (41.0)	Use of glibenclamide, which can cause prolonged hypoglycaemia
Medicine not useful at all	7 (33.3)	27 (5.0)	17 (11.6)	4 (12.5)	32 (4.7)	15 (9.6)	Use of meprobamate, for which safer alternatives are available
Prescribing omissions	4 (19.0)	29 (5.4)	16 (10.9)	5 (15.6)	43 (6.4)	18 (11.5)	Omitting to prescribe osteoporosis prophylaxis for a patient using high doses of corticosteroids for a long period
Incorrect duration of therapy	2 (9.5)	10 (1.9)	7 (4.8)	0	6 (0.9)	3 (1.9)	Prolonged use of hypnotics
Unnecessary therapeutic duplication	0	39 (7.3)	3 (2.0)	1 (3.1)	40 (5.9)	5 (3.2)	Simultaneously use of different benzodiazepines
Form of medication not suitable for the elderly	0	12 (2.2)	3 (2.0)	2 (6.3)	16 (2.4)	0	Use of immediate release nifedipine capsules
Suitable for the indication?	0	53 (9.9)	2 (1.4)	0	111 (16.4)	3 (1.9)	Patient uses an oestrogen preparation regularly used for complaints caused by menopause
Adherence (too much or too little use)	1 (4.8)	57(10.6)	1 (0.7)	1 (3.1)	74 (10.9)	2 (1.3)	Patient uses more oxazepam than prescribed
Contra-indication known	2 (9.5)	9 (1.7)	1 (0.7)	6 (18.8)	12 (1.8)	3 (1.9)	Use of amiodarone by patient suffering from hypothyreosis
Drug-drug interaction known	1 (4.8)	60(11.2)	0	0	60 (8.9)	0	-
Treatment of side effect of other medicine	0	84(15.6)	0	2 (6.3)	77 (11.4)	0	-
Others	1 (4.8)	88(16.4)	0	11 (34.4)	118 (17.5)	1 (0.6)	Use of a combination of amlodipine and losartan for a patient with oedema. Stop amlodipine and increase losartan dosage
Total	**21 (100)**	**537(100)**	**147 (100)**	**32 (100)**	**676 (100)**	**156 (100)**	**-**
Number of rec. per patient	**0.06**	**1.53**	**0.42**	**0.08**	**1.75**	**0.40**	**-**
Total number	**705**			**864**			**-**
Number of rec. per patient	**2.01**			**2.23**			*p*=0.059 Difference=0.229 95% CI -0.467-0.009

The pharmacy assistants could not determine from the pharmacy records whether 883 of the recommendations presented in table 2 (56.3% of all recommendations) had been acted on or not. Most problems concerned doubts about the correctness of the indication and doubts whether routine checks were performed.

In the comparisons that followed, only the 303 recommendations with direct clinical relevance were included. For 18 recommendations problems were solved or the particular medicine had been discontinued before the intervention started; these recommendations were excluded. Another 16 recommendations were excluded from the 6-month measurement because the particular patients were excluded from the study. Thus, 269 recommendations were included in the analysis of the 6-months measurement. A further five recommendations were similarly excluded for the 9-months measurement, leaving 264 recommendations.

Medication changes following clinically-relevant recommendations made by pharmacists

Table 3 presents the number of medication changes following clinically-relevant recommendations. Significantly more medication changes were initiated in the case-conference group than in the written-feedback group (42 vs 22, $p = 0.02$). This difference is also present in the maintained medication changes at 6 months after the treatment reviews (36 vs 19, $p = 0.02$). For medication changes maintained until 9 months after the treatment review, the difference between the groups was no longer significant (33 vs 19, $p = 0.07$).

Table 3. Number of medication changes following recommendations with clinical relevance

Time	Medication changes		X^2
	written feedback, n	Case conferences, n	p-value
Measurement at 0-6 months and 6-months	128	141	-
0-6 months after medication reviews (initiated medication changes, all attempts, whether or not sustained)	22	42	*p=0.016*
6 months after medication review (sustained changes)	19	36	*p=0.022*
Measurement at 9-months	126	138	-
Changes sustained until 9 months after medication review	19	33	*p=0.070*

Percentage of clinically-relevant recommendations followed was examined as a secondary outcome measure. Significantly higher percentages of these recommendations led to initiated medication changes in the case-conference-group than in the written-feedback group (29.8% vs 17.2%, $p = 0.02$). This was also seen for the percentage of maintained medication changes at 6 months after the treatment reviews (25.5% vs 14.8%, $p = 0.03$). At

the 9-month measurement there was no statistically significant difference (23.9% vs 15.1%, $p = 0.08$).

Cost evaluation

Pharmacists in the case-conference group spent significantly more time on this intervention (with accompanying increase in costs) than pharmacists in the written-feedback group. This was also true for GPs who kept time logs. Unfortunately only 37% of all GPs kept time logs: 42.5% in the case-conference group and 30.5% in the written-feedback group.

Changes in patient pharmacy records that were attributed to the treatment review led to a modest decrease in medicine costs. Although these benefits were slightly greater in the case-conference group, this difference did not reach statistical significance (Table 4).

Table 4. Costs and savings as caused by the intervention (multilevel statistics), all recommendations are included.

		Cost changes per patient, € [1]		p-value	Difference (95% CI)
		written feedback (n)	Case conferences (n)		
Costs caused by time expenses on the total process of medication review	Pharmacist	9.69 (350)[2]	15.03 (387)	$p = 0.001$	5.27 (2.21-8.34)
	GP[3]	6.22 (97)	8.68 (163)	-	-
Savings due to medication changes at 9 months after intervention		-4.33 (320)	-7.78 (365)	$p = 0.357$	3.44 (-3.89-10.77)
Yearly savings in medicine costs for each year that the medication change persists		-7.79 (320)	-12.24 (365)	$p = 0.443$	4.44 (-6.90-12.81)
Net expenses at 9 months after medication review (including pharmacy costs and savings on medicines)		5.52 (319)	7.23 (365)	$p = 0.655$	1.72 (-5.80-9.23)
Net expenses at 9 months after medication review (including pharmacy and GP costs and savings on medicines)		14.22 (89)	13.71 (153)	-	-

[1] Positive number means expenses, negative number means savings
[2] For one patient the time log from the pharmacy got lost, so this patient was excluded from this analysis.
[3] From GPs, time logs for only 37% of all participants were received.

The expenses and cost benefits of the intervention partially cancelled each other out. The extra savings in the case-conference group offset a part of the extra costs due to extra time needed by the pharmacists and GPs in this group. There was no significant difference in remaining net costs including pharmacy time expenses and savings on medicine costs between the two intervention groups. For the remaining net costs including pharmacist time expenses, GP time expenses, and savings on medicine costs, no statistical testing was performed because of the small number of participants. The results shown in table 4 do not seem to indicate differences in remaining costs including pharmacy-time, GP-time and savings on medicine costs.

Discussion

Summary of main findings

In this study, community pharmacists performed treatment reviews for 738 patients and feedback was given to GPs. Feedback in personal contact between the pharmacist and the GP (case conferences) led to significantly more medication changes following recommendations of clinical relevance.

Medicine costs were also influenced by the interventions. Both types of intervention showed modest savings regarding medicine costs. The slightly greater savings seem to cover extra costs caused by pharmacist and GP time expenses in the case-conference group.

When the effect of the intervention was examined over time, differences between the intervention groups were shown to decrease gradually.

Strengths and limitations of the study

The process of medication reviews was studied in a large sample of pharmacists and GPs by means of a cluster controlled trial, and a cost-evaluation was included. Despite these strengths, this study was not without limitations. Only medication changes weren taken into account; therefore, a considerable number of recommendations with solutions other than medication changes were not examined. For example, the effect of some drug-drug interactions can be monitored by checking blood pressure or other parameters, but it was not checked whether such actions were taken. This loss of data undoubtedly reduced the ability to detect differences, and made this analysis fairly conservative.

Time logs were received from only 37% of participating GPs, and as the calculations that include GP time expenses are based on a small number of patients, they have to be interpreted with some reservations. Statistical tests were not performed on these figures.

GPs were chosen by the participating pharmacists (convenience sample). It is possible that only GPs with whom the pharmacists had the best professional relationships were included, which could have led to an over-rating of the effect of these interventions.

Comparison with existing literature

This study indicates that treatment reviews involving personal contact (case conferences) lead to more medication changes than an intervention including only written feedback. Studies considering improvement of prescribing practice report similar findings[15-18]. As the extra costs of this approach seem to be covered by the extra savings on medicine costs, the case-conference approach is recommended in practice.

The persistence of medication changes over time was also investigated. Eighty-six per cent of the medication changes were maintained for at least 9 months after the treatment

review in the written-feedback group, and 79% in the case-conference group. Other studies have shown that 84% [19] and 64% [20]of the interventions were maintained until six months after the intervention. Another study has shown that 90% of recommendations made by a clinical pharmacist remained implemented up to one year after the patient interview[21].

Savings on medicine costs were also studied. Although older patients included in this study were using at least five prescription medicines, prescribing omissions were identified. Studies concerning the quality of pharmaceutical care have also observed omissions[2,22-26]. In a number of cases, these prescribing omissions were for newer, more expensive medicines (for example, bisphosphonates and proton-pump inhibitors); therefore, it is not surprising that the medicine costs did not decrease much. Some studies have found differences in costs after medications reviews[13,19,27-30], while others have not [4,31-33].

Implications for future research

At the time the study was planned, a number of trials were performed considering the effectiveness of treatment reviews. In the trials published at the time, no statistical difference in health status or patient satisfaction was found[3-6]. As a result of the information from the literature and because the current study examined the differences between two procedures for treatment reviews (case conferences versus written feedback), it was decided not to make the study more complicated by measuring health status at patient level. However, positive trends in clinical outcomes were found in a later study by Sorensen et al.[34]

Met opmaak

Verwijderd: [34]

In a systematic review some evidence was found that pharmacist-led interventions incorporating a medication review are effective in reducing hospital admissions[35], and in a further study concerning older people living in care homes a reduction in the number of falls was found when performing clinical medication review[30].

Further research is needed to examine the clinical consequences of treatment reviews and medication reviews. To measure the clinical consequences, health status, health-related patient satisfaction, numbers of falls, hospital admissions, and mortality rates could be used. These studies should include large populations of older people because medication is just one of the parameters that influences these clinical outcome measures. These kinds of studies have already been carried out for home-based interventions after hospital admissions to prevent re-admissions[36,37] and variable and unexpected results.

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Chapter 7

Comparison of two methods for performing treatment reviews by pharmacists and general practitioners for home-dwelling elderly people

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Abstract

Rationale, Aims and objectives: There is room for improvement in pharmacotherapy for elderly outpatients. Studies have shown that collaborating health-care professionals (e.g. pharmacists in cooperation with general practitioners) are able to resolve prescription-related pharmaceutical care issues by means of treatment reviews. The aim of the study was to describe the feasibility of two methods for treatment review (results were given to the GP either in case-conferences or in written feedback), and to determine if and how the process of treatment review can be improved.

Setting: Local pharmacists and general practitioners (GPs) cooperated in performing treatment reviews for outpatients aged 75 years or more who were using five or more medicines chronically.

Method: Written questionnaires, structured telephone interviews, and analysis of various features of the treatment reviews that were recorded during the intervention study.

Results: The pharmacists in the case-conference group made more recommendations to the GPs (non significant). Significantly more recommendations were identified by the pharmacists themselves in the case conferences group. Health-care professionals accepted an intervention with personal contact in case conferences better than an intervention with feedback in writing. They were more positive about the process of treatment review presented personally, although there were not always as many medication changes as they had hoped for. They also had concrete suggestions for improving the intervention, such as using a combination of written feedback and case conferences, and reserving the case conferences for the most complex cases.

Conclusions: Treatment reviews for the elderly in normal primary care are feasible. Health-care professionals agree that the process for treatment review can be improved.

Introduction

The elderly use more medicines than younger people because they have more chronic diseases. In a previous study, we found that almost all pharmacotherapy for the elderly needs improvements.[1] Performing treatment review would be an aid to making such improvements.[2-5] These treatment reviews can be performed by primary care professionals, e.g. pharmacists in cooperation with general practitioners (GPs).

We examined the effects of two methods of treatment review in a cluster controlled trial [6] that compared case conferences involving both pharmacists and GPs with written feedback from the pharmacist to the GP. We examined the supplemental costs to determine whether the savings on medicine costs offset the additional costs of the more time-consuming case conferences. Our study shows that treatment reviews with case conferences lead to better results than treatment reviews with written feedback when taking recommendations with direct clinical relevance in to account. Further, the net costs of the personal contact model did not seem to be greater than those of the written feedback model. It was noted that the effect of the intervention decreased over time.

From our and other researchers' studies, we concluded that performing treatment reviews for elderly patients is valuable.[3;5;6] In the present in-depth process evaluation, we describe the perspectives and experiences of the GPs and pharmacists involved in treatment reviews. First, we examine the feasibility of having these health-care professionals embed such treatment reviews in daily medical practice. Second, we elaborate on opportunities for improvement of the process of treatment reviews. The results give rise to recommendations to make treatment reviews more suitable for use in daily practice.

Methods

To study the feasibility of the treatment reviews, we analysed data about the use of treatment reviews and asked the opinions of the participants in written questionnaires and structured interviews. In this way, both objective and subjective data were used to determine feasibility.

Setting

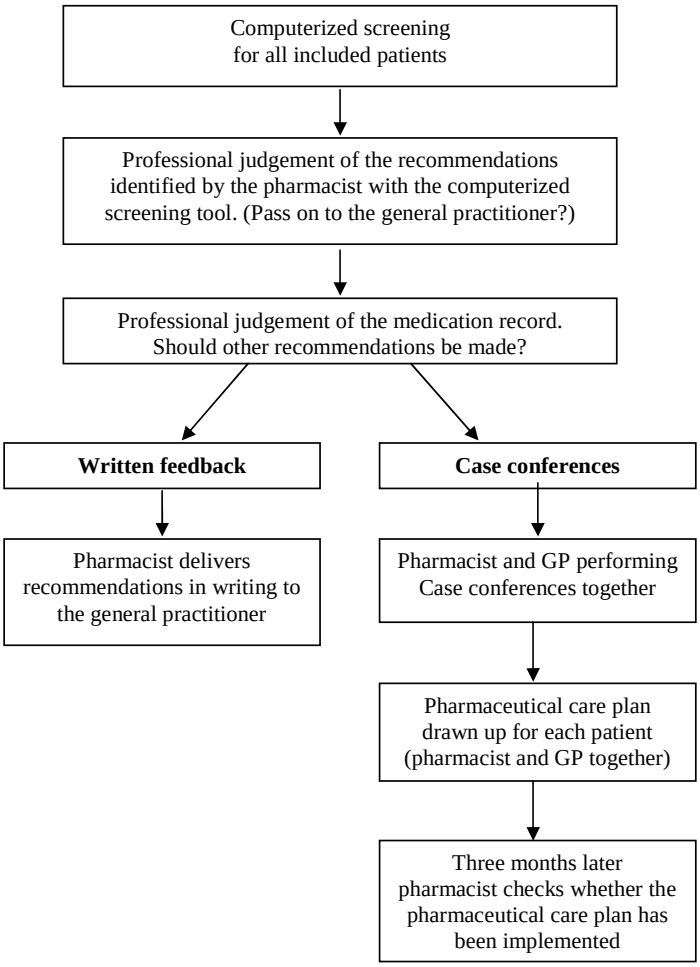
In a primary care setting, treatment review were performed by 28 pharmacists and 77 GPs for 738 elderly people (aged 75 years or more) using 5 or more medicines chronically.

Intervention

In both intervention groups, the pharmacists used our computerized screening tool to perform treatment reviews.[6] They had to decide which of the recommendations highlighted by the computerized screening tool should be given to the GP, and whether additional recommendations concerning the pharmacotherapy of these patients should be pointed out.

The organizational models of two intervention groups differed (Figure1):

Figure 1. Flow diagram of the intervention programme



- *Feedback in writing*

  The pharmacists listed all recommendations for each patient and delivered them to the GP's office. The pharmacist did not follow up.

- *Case conferences*
  The pharmacist and the GP discussed all recommendations as well as other concerns about the patients (if any). The pharmacist and the GP together drew up a pharmaceutical care plan in which they noted who was responsible for the activities in the plan. Three months later, the pharmacist checked whether these activities had been carried out.

During the intervention study, clinical relevance was assessed for all recommendations that were passed on to the GPs. Recommendations were classified as:

- *Clinically relevant:* the recommendation leads to improvement in the patient's general health.
- *Potentially relevant*: relevance depending, for example, on the medical condition of the individual patient.
- *Clinically irrelevant*: the recommendation does not lead to improvement of the patient's general health.

For most of the recommendations identified by our computerized screening tool, clinical relevance was judged on the basis of our earlier in-depth analysis of pharmacotherapy,[1] or on the literature[7-10] for some of the remaining problems. For the recommendations that the pharmacists identified themselves, clinical relevance was based on our in-depth analysis or was determined by an expert panel during the present study.

The expert panel consisted of a GP, a community pharmacist, a geriatrician, and a clinical pharmacist. Clinical relevance was determined in a consensus method, which consisted of a round in writing followed by a round on the telephone. During the consensus meeting on the telephone, the experts discussed all differences until they reached consensus about the clinical relevance of the particular recommendation.

Variables

Use of treatment reviews in practice

- The number of recommendations made for each patient: the average number of recommendations for each patient was recorded for each intervention group separately.
- The number of clinically relevant recommendations: the average number of recommendations with direct clinical relevance for each patient was recorded for each intervention group separately.
- Origin of the recommendations passed on to the GP: the overall percentage of recommendations identified by the pharmacist themselves was determined within both intervention groups.

- Time spent in performing treatment reviews: the overall time per patient was determined for each intervention group.

Opinions about feasibility of treatment reviews

Written questionnaires were sent to all participating health-care professionals (pharmacists and GPs). Reminders (including a new copy of the questionnaire) were sent after 2 and 5 months. The questionnaire included questions about:

- Views and opinions of the results of the treatment review: did the results outweigh the time spent? (GPs and pharmacists)
- Opinion about time spent: did the performance of this intervention cost more or less time than expected (GPs).
- Opinion of health-care professionals about the applicability of this intervention for all elderly patients in their practices (GP and pharmacists).

The researcher interviewed by telephone 18 randomly selected pharmacists and 16 randomly selected GPs, both evenly divided over the intervention groups. In the structured interviews, the researcher asked about ways to improve the treatment review method:

- Stimulating factors for performing treatment reviews (GP and pharmacist)
- Impeding factors for performing treatment reviews (GP and pharmacist)
- Difficulties in effecting medication changes (GP)
- Recommendations to optimize the process of treatment review (GP and pharmacist).

Practice characteristics

- General practice characteristics (health-care centre or solo practice, number of patients in practice, proportion of elderly patients in practice, full-time or part-time employment of staff, start of employment in this general practice)
- Pharmacy characteristics (number of pharmacy assistants employed, number of pharmacists employed, proportion of elderly pharmacy, number of prescriptions a day, year of graduation of the participating pharmacist).

Analysis

Types of problems and recommendations were processed manually and entered into an MS-ACCESS database. When medication changes took place, the changes were entered in the database along with the clinical relevance of the recommendations and their origins[6]. This database was analysed with SPSS 12.0 (SPSS, Illinois).

Results of the written questionnaires were entered into an MS-ACCESS database, which was analysed with SPSS 12.0 and used to generate the statistics. Results of the structured telephone interviews were literally noted and categorized.

Results

Analysis of use of treatment reviews

More recommendations per patient were passed on to the GPs in the case-conference group that in the written feedback group, although this difference is not statistically significant. The number of recommendations with direct clinical relevance per patient is almost equal for both intervention groups (Table 1).

Table 1 shows that significantly more recommendations were identified by the pharmacists themselves in the case–conference group than in the written feedback group. In our intervention study, we saw that this category of problems was solved significantly more often than the familiar problems identified by the computerized screening tool.[6]

Furthermore, the origins of the recommendations made by the pharmacists within both intervention groups varied greatly; this is also true for the clinical relevance of the recommendations made.

Table 1. Use of treatment reviews as performed by pharmacists

		Case conferences	**Written feedback**	**Chi square statistics**
Pharmacists		*n* = **15**	*n* = **13**	
Average number of recommendations passed on to the general practitioner per patient (number of patients)	All recommendations	2.23 (387)	2.01 (351)	(p = 0.059)
	Clinically relevant recommendations	0.42 (387)	0.40 (351)	(p = 0.753)
Sorts of recommendation made by the pharmacists (total number of recommendations)	% of recommendations of direct clinical relevance	18.1 (864)	20.9 (705)	(p = 0.165)
	% of recommendations identified by the pharmacists [1]	41.7 (832)	34.2 (682)	(p = 0.003)
Range in percentages of sorts of recommendations made by the pharmacists	Recommendations of direct clinical relevance	0-36	13-34	-
	Recommendations identified by the pharmacists	16-76	1-74	-

[f]Recommendations regarding compliance were not included in this comparison

Pharmacists spent more time on the intervention than GPs did. Health-care professionals gave more of their time in the case–conference group than in the written feedback group (Table 2). However, the sample of GPs was too small to make assumptions about all participating GPs and no statistical testing was performed for this group of health care professionals. For both groups of health-care professionals, the variability within the intervention groups was substantial.

Table 2. Time expenses shown in multilevel statistics

		Case conferences	Written feedback	Multilevel statistics
Average time in minutes spent on intervention per patient (number of patients for which a time log was kept)	General practitioners	10.4 (163)	7.46 (97)	- [1]
	Pharmacists	18.0 (387)	11.6 (350)	$p = 0.001$
Range in time expenses in minutes per patient (number of professionals that kept time logs)	General practitioners	3.7-18.5 (17)	2.1-16.0 (11)	-
	Pharmacists	10.3-43.0 (15)	3.2-33.1 (13)	-

[1] Because of the low number of time logs kept by GPs we did no statistical testing on the time spent by GPs

Written questionnaires and structured interviews

We received 27 (73% response) completed questionnaires from the GPs in the written feedback group and 37 (93% response) from those in the case-conference group. The pharmacists returned all the questionnaires (response 100% in both intervention groups).

General practitioners in the case-conference group were more positive about the results of the treatment reviews than the GPs in the written feedback group (Table 3). They found that it was useful and that it had a positive impact on the pharmacotherapy. Despite the fact that case conferences were more time consuming and took more time than expected, the GPs in this group were also more positive about the feasibility of this approach in daily practice.

Table 3. Written questionnaires: general practitioners' opinions about feasibility of treatment reviews for the elderly

	Case conferences	Written feedback
Number of GPs (Percentage of total included in the study)	**37** (93)	**27** (73)
Pharmacotherapy for patients is optimal after this intervention	24.3%	14.8%
Performing treatment reviews has led to medication changes	54.1%	48.1%
Performing treatment reviews for the elderly took more time than expected	11.1%	3.7%
Implementation of treatment reviews for the elderly in daily practice is impossible	2.7%	7.4%
Treatment reviews for the elderly can be implemented in daily practice, but a reasonable amount of time should be reserved	56.8%	59.3%
Treatment reviews for the elderly are only feasible with a financial remuneration	10.8%	11.1%
If they are spread over the entire year, it is possible to perform treatment reviews for the elderly	24.3%	14.8%

The results for the pharmacists in the case-conference group were similar. The pharmacists in general were slightly more positive about feasibility in daily practice. One of the participants in the written feedback group thought that it is impossible to implement treatment reviews for the elderly in daily practice, but none of the pharmacists in the case-conference group shared this opinion. Four pharmacists in the case-conferences group thought that treatment reviews for the elderly should be possible if they were spread over the year. Only two pharmacists in the written feedback group shared this opinion. Most

pharmacists, however, thought that implementing treatment reviews in daily practice is possible, but a reasonable amount of time should be reserved for them (9 pharmacists in the case-conference group and 8 in the written feedback group). Two pharmacists in each group thought that this activity could only be implemented in daily practice if it was paid for by health-care insurance companies.

Factors influencing the results of the treatment reviews

Good collaboration and motivation were mentioned as stimulating factors for treatment reviews, but some participants thought the personal relationship between GP and pharmacist was an interfering factor. Some participants named pharmacotherapy audit meetings as a useful tool for starting the process of performing treatment reviews for the elderly. The pharmacists liked the input they got from the computerized screening tool.

There were several difficulties in changing medications for these elderly patients. One was the fact that if a medication has been initiated by medical specialists, GPs are not inclined to change the prescription. Another difficulty was that the patients are not always cooperative, particularly when discontinuation of hypnotics is suggested. A frequently mentioned problem is the amount of time needed for treatment reviews, as reported by GPs and pharmacists in both intervention groups (Table 4).

Recommendations for introducing this intervention in daily practice

The participating pharmacists and GPs made the following recommendations during the structured interviews.

- Focus on a selection of patients with relatively many problems, or with many medicines, as these patients will benefit most from quality improvement interventions.
- Some types of problems do not require face-to-face contact between pharmacists and GPs; they can be solved by feedback in writing (e.g. prolonged use of hypnotics). Other types of problems (more complex problems or more complex cases) require discussions about indications, etc. In practice, this could lead to a combination of both forms, in which only complex cases or problems are discussed, while the remaining ones are dealt with in writing.
- Make it a continuous project in which specific groups of patients (e.g. starting with diabetes mellitus patients, followed by rheumatoid arthritis patients, etc.) are included in different periods of time.
- Include patients living in nursing homes and/or homes for the elderly.

Table 4. Structured interviews: stimulating and interfering factors for treatment reviews

	Case conferences	**Written feedback**
Number of GPs	**8**	**8**
Number of pharmacists	**9**	**9**
Stimulating factors (GPs)	Good collaboration with pharmacy (1) Pharmacotherapy audit meetings (1)	- (none named)
Stimulating factors (pharmacists)	Motivation and cooperation of GP (3) Pharmacotherapy audit meetings (1) Computerised screening tool (1)	Computerised screening tool (3) Participation by whole pharmacotherapy audit meeting group (1) Participation in research project (1)
Interfering factors (GPs)	Time expenses (2) Specialists' prescriptions(1) Organizational factors (1)	Time expenses (2) Influence of patients (2) Fear of medication changes causing confusion for the patient (1) Changing medications after years of use seems like admitting that prescribing was not always optimal (1)
Interfering factors (pharmacists)	Relationship with general practitioner (3) Time expenses (1) Practical problems linking patients to general practitioners (1) Practical problems switching between computer programmes (1)	Time expenses (2) General practitioner's supposed lack of time (1) Lack of knowledge of the indication for prescribed medicines (1) No response from general practitioner (1) Specialists' prescriptions (1) So few spectacular problems found is not motivating (1) Practical problems linking patients to general practitioners (1) Practical problems printing data from computerized screening tool (1)
Difficulties in effecting proposed medication changes (general practitioners)	Influence of patients (2) Fear of medication changes causing confusion for the patients (1) Organizational factors (repeat prescribing) (1) Specialists' prescriptions (1)	Influence of patients (3) Specialists' prescriptions (4)

Discussion

Main findings

Pharmacists in the case-conference group spent more time on the intervention than pharmacists in the written feedback group. The pharmacists in the first group identified more recommendations of which more were identified by the pharmacists themselves than the pharmacists in the latter group.

Pharmacists and GPs were both positive about performing treatment reviews and the feasibility of implementing the process in daily practice. Health care professional in the case–conference group were generally more favourable to this, although not all of them found that the results justified the time spent.

Both positive and negative factors influenced the results of the intervention. Cooperation and personal relationship between the pharmacist and the GP were said to be both positive and negative in performing treatment reviews. The time required and

specialists' prescriptions were named as negative factors influencing the results of the intervention.

The participating health-care professionals did have several recommendations for optimizing treatment reviews. For example, they suggested a combination of written feedback and case conferences; they thought it sufficient to discuss only the most complex cases and use written feedback for the rest.

Comparison with existing literature

General practitioners saw the patients themselves as one of the reasons why some medications were not changed. Patients were not always inclined to stop using medicines that they had used for a long time; this finding is consistent with other studies.(11) This problem is well known in regard to hypnotics; it is difficult to stop using benzodiazepines without specific interventions.[12-14] With regard to changing medication prescriptions initiated by specialists,[11;15] we believe that, although GPs often say that this particular part of their prescribing behaviour cannot be changed, they also have a responsibility when specialist-initiated prescriptions are repeated.[16]

Limitations

The GP response rates were low for the questionnaires and the time logs, particularly in the written feedback group. Perhaps the GPs in this group were not as motivated as the others. As it is likely that the non responders had less positive experiences with the interventions, the actual differences between the two groups might even be more pronounced than our findings show.

Recommendations for daily practice and further research

In our study, usage of the treatment reviews varied greatly, possibly because of differences in the quality of pharmacotherapy at the beginning of the study, as well as the degree of dedication and experience in treatment review of the health-care professionals. It seems advisable to introduce the process of treatment reviews and pharmacotherapy for the elderly in a pharmacotherapy audit meeting to optimize involvement and to inform participating health-care professionals.

In some instances, GPs reported that the intervention had a spill-over educative effect. They learned about optimizing medication prescriptions for the elderly, both in the cases discussed and for other cases with similar pharmacotherapy. In some instances, the GPs decided not to change the medication, but reported that they would bear the newly acquired knowledge in mind when treating other patients. Further research is needed to examine the educational effect of such interventions in daily practice.

Adaptations should be made in order to implement such treatment reviews, for example, by focusing on specific indications, or on patients using many medicines. Finally, we recommend a combined treatment review with a discussion in person for the more complex cases, while recommendations for more evident cases might be given in writing. However, this requires the pharmacist to distinguish most complex and important recommendations and those that the GP already knows about. Further research is needed to study the supplemental effect of such changes in the process of treatment reviews.

Treatment reviews, how to perform them

If we combine the information from the intervention study and this process evaluation, we can identify characteristics that should ideally be present when performing medication reviews.

- It seems logical to start the process of treatment review with a pharmacotherapy audit meeting that focuses on polypharmacy and on special considerations for prescribing for the elderly.
- The medication reviews are performed by a pharmacist with supported by a computerized screening tool. The results of the treatment reviews are given to the GPs in case conferences for the most complex cases, and the more familiar recommendations can be given in writing or are talked about briefly.
- It seems advisable to draw up a pharmaceutical care plan that records the names of those responsible for each task. Three months after the meeting, the pharmacist checks whether all activities have been carried out.
- Treatment reviews should be repeated periodically because
    1. The effect of the intervention diminishes in time.
    2. Use of other medicines or disorders can be identified in a reviewed case so that evaluation has to be repeated.
    3. Pharmacotherapeutic guidelines are continuously improving, which gives rise to new points of attention for a patient with the same medicines.
    4. There will be new cases in the population that must be considered for treatment review.

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Chapter 8

General discussion

In the general discussion of this thesis the main findings from our research project are highlighted and the strengths and limitation of the individual studies are discussed. Furthermore the implications for our studies for health care professionals, policy makers and pharmacy practice researchers are elaborated.

Main findings

Part I Problems associated with elderly and use of medicines

In a first study among elderly > 75 years using 4 medicines or more we found that in two thirds of the participants user-related pharmaceutical care problems could be observed. User related pharmaceutical care problems of potential clinical relevance were identified in a quarter of the study objects. High numbers of problems were associated with the use of medicines with complex administration forms (e.g. eye drops and inhalation devices). Different risk factors could be identified for problems in general and for problems with direct or potential clinical relevance. These risk factors can be used in daily practice to identify patients at risk of user related pharmaceutical care problems.

In the study regarding prescription related problems we observed high numbers of problems of potential clinical relevance. For almost all elderly patients recommendations could be made concerning prescribed medicines. For one third of the patients at least one recommendation with direct clinical relevance could be made; meaning that following the recommendation will lead to improvement in general health. For two thirds a medicine may need to be added to optimise pharmacotherapy. One quarter of these prescribing omissions were of direct clinical relevance.

In the study regarding our composite screening tool we found a number of existing screening tools in the literature as well as many studies concerning geriatric prescribing and medication reviews. All existing screening tools proved to have some limitations, therefore we developed a composite tool for medication review of patients in primary care. A wide range of issues that should be taken into account when reviewing pharmacotherapy is included in this new tool.

In our study in the Rotterdam study database we saw that hypoglycaemia is seen in 1 out of 12 patients during the study period. The risk was four times higher in insulin users with or without oral agents (39.11 and 39.04 per 1000 person years) than in users using only oral antidiabetics (9.88 per 1000 person years). In the multivariable analyses use of insulin and renal impairment (both associated with an increased risk) remained significant for all users of hypoglycaemic agents. Use of tolbutamide (associated with a decreased risk) and use of medicines having an influence on CYP2C9 (associated with a increased risk) remained significant for users of sulfonylurea derivatives. As the risk for hypoglycaemia is greater in insulin users than in users of oral antidiabetic drugs, it seems

particularly relevant that elderly insulin users can adequately recognize and rectify upcoming hypoglycaemic events. As the risk of hypoglycaemia is also greater in elderly users of glibenclamid than in users of tolbutamid, the latter sulphonylurea derivative is the drug of choice in this drug class. Finally, more attention should be paid to interactions between sulphonylurea derivatives and CYP2C9 modifying drugs (such as co-trimoxazole).

Part II Improving medication safety in the elderly

After identification of problems as seen in elderly using medicines we searched for possible solutions. As prescription-related problems were observed most frequently and as many are of potential or direct clinical relevance, we were interested in interventions specifically aimed at improvement of prescribing for the elderly on polypharmacy. In so called “treatment reviews” pharmacotherapy for individual patients is screened and in most instances recommendations for improvement of pharmacotherapy can be made.

Our intervention study aimed at improving the collaboration between GPs and pharmacists. In particular we studied if a more labour intensive intervention leads to better results. A cost-evaluation was performed as well. We found that performing treatment reviews accompanied by personal communication in case-conferences leads to higher numbers of medication changes with direct clinical relevance than treatment reviews with written feedback only. Furthermore, supplemental costs as caused by case-conferences seem to be covered by higher savings on medication costs.

In our process evaluation we found saw that the health care professionals also preferred treatment reviews with case conferences, it improves the collaboration between the health care professionals, since both health care professionals can show their own expertise. Both GPs and pharmacists had recommendations for optimising the use of treatment reviews in daily practice. For example, they recommended a combination of case conferences and written feedback, case conferences for complex patients while for other patients written feedback will be sufficient.

Strengths and limitations

The studies concerning user related problems and prescription related problems were performed in a population of elderly (75 years or over) using 4 or more medicines chronically. During these studies we saw that the elderly were having practical problems and that prescribing in this population could be improved, nevertheless we saw an increase in the number of problems when higher numbers of medicines were taken.

Although user related problems were studied before, our study is the first one that includes all kinds of user-related problems in one study. Because clinical relevance of the

problems was variable we determined the clinical relevance of the indicated problems and made separate risk models for all problems and for problems with potential clinical relevance. Although we tried to study the user-related problems as reliably as possible, there were some limitations to our study. We relied on self-reports of problems, which may have led to an underestimation. Furthermore selection bias may have occurred in the response of the invited participants. Participants familiar with non-compliance may be less inclined to take part in a study concerning drug-taking habits. We concluded that the finding of one quarter of elderly patients (using 4 or more medicines) having potential clinically relevant user-related problems is rather conservative.

The study regarding the prescribing quality of polypharmacy is the first in-depth analysis by a large expert panel and focuses on a wide and comprehensive set of prescription related points of attention. This analysis was performed by means of a consensus approach, which entails the risk that some panel members are more influential than others. However we did not notice such influences. Furthermore, although a sample of 100 patients is rather large for a comprehensive analysis of prescribing, some problems that occur rarely may have been underrepresented in this sample.

Our new tool for medication review gives an overview of all different types of problems that should be taken into account in the implicit reviewing of medication patterns. Articles were identified from Medline following a free text search on the term “medication review(s)”, supplemented by an incremental search strategy that comprised manual searching of previously collected literature, on-line searching for additional papers of the research groups prominent in this field and manual searching of the bibliography of useful articles. Probably most relevant articles and many examples were included in this tool, however, it is not a systematic review.

The incidence of hypoglycaemic events as determined in our study in the Rotterdam study database is probably an underestimation of the total number of hypoglycaemic events in the study population. This is partly caused by GPs who will use portable blood glucose measuring equipments in acute situations, these values were not included in our study. Furthermore, our study did not take in that more experienced diabetic patients may selfadminister a source of glucose to cope with an upcoming hypoglycaemic event. Other limitations of this study were the limited number of cases and the low frequency of some of the cofactors. To overcome these last limitations this study should be repeated in a database containing larger numbers of diabetic patients using all kinds of medicines.

We studied the process of medication reviews in a large sample of pharmacists and GPs by means of a cluster controlled trial. Furthermore a cost-evaluation was performed. There were some limitations to this study. We only took medication changes into account, so a considerable number of recommendations with solutions other than medication changes

were not taken into account. This loss of data undoubtedly reduced our ability to detect differences, and made our analysis conservative.

Furthermore we did not measure outcomes at the patient level. In the trials that had been published at the time, no statistical differences (nor positive nor negative) in health status or patient satisfaction were found [1-4]. Because of the information from the literature and because our study was indicated at the differences between two procedures for treatment reviews (case conferences versus written feedback) we decided not to make our study more complicated by measuring health status at patient level. Afterwards, however, positive trends in clinical outcomes were found in a study by Sorensen [5]. In a systematic review some evidence was found that pharmacist-led interventions incorporating a medication review are effective in reducing hospital admissions[6] and in another study concerning elderly living in homes for the elderly a reduction in the number of fall was found when performing clinical medication review[7]. New studies should measure the impact of our outpatient approach on patient outcomes.

Our process evaluation is based on questionnaires, structured interviews and various features of treatment reviews recorded during the intervention study. The combination of these data gives more insight in the process of treatment review than the different sources individually. There were some limitations to this study, the response rates of general practitioners were low for the questionnaires and time logs, in particular in the written feedback group. Perhaps the general practitioners in the written feedback group were not as motivated as the GPs in the group with case conferences. As it is likely that the non-responders may have had less positive experiences with the interventions, the actual differences between the two groups might even be more pronounced than our findings showed.

Implications for improving medication safety

When performing treatment reviews some problems can be identified retrospectively, but as far as this is possible prevention is preferable. In daily practice older age should be considered a contra-indication for certain medicines and groups of medicines, whereas for other medicines dosages should be adjusted. These types of problems can be tackled easily by means of alerts in electronic pharmacy practice systems (and general practice systems). Nowadays such alerts are not yet included because no official list containing medicines not suitable for use by the elderly or dosage adjustment needed for the elderly is available for the Dutch primary care setting. We propose that a group of experts in the field of geriatric prescribing and dispensing composes a national list containing medicines not suitable for use by the elderly or dosage adjustment needed, specifically aimed at the situation in the Netherlands.

In our study considering drug-induced hypoglycaemia we identified risk factors that can be used to identify patients at risk of hypoglycaemic events. By using these risk factors in daily practice it may be possible to reduce hospitalisation caused by hypoglycaemia. In 2003 a guideline for prevention of NSAID related gastro-intestinal complaints was launched in the Netherlands[11], yet NSAIDs still are identified as one of the drug-classes causing gastrointestinal bleedings leading to hospital admissions in a study that was performed in 2006 [12]. So just identifying risk factors and take them up in guidelines is not enough to prevent hospital admissions. Guidelines should be implemented in daily practice by means of well developed and effective implementation programs[13]. These programs should ideally consist of dissemination of the guidelines by means of professional publications, supplemented by personal communications (education programs, audit meetings or even visits from advisors)[13-16]. Optimal implementation will be reached when risk factors related to drug-induced hypoglycaemia are included in pharmacy and general practice systems, and electronic alerts will be given in daily routine.

Although we looked at home-dwelling elderly in our studies, other studies have shown that performing treatment reviews will also be useful for patients living in nursing homes or homes for the elderly [7,17-19]. We excluded persons living in homes for the elderly because they get help with managing and administering their medicines. Furthermore, for high amounts of elderly living in nursing homes repeat prescriptions are requested by the pharmacist by means of a medication overview that can be signed by the GP. At this time most pharmacists and GPs do have a regular look at the complete pharmacotherapy for these patients. A recent study considering drug-induced hospitalisations in the Netherlands indicated patients living in nursing homes or homes for the elderly being at increased risk of potentially avoidable drug-induced hospitalisation[12]. Hence we recommend performing treatment reviews for these categories of patients as well.

Although we decided to focused our research project on improvement of geriatric prescribing, and hence did not study interventions aimed at user-related problems, we think that patients can benefit from a medicine consultation with a pharmacist. This has been proved in studies performed by others; the numbers of user-related pharmaceutical care problems were reduced by performing medicine consultations [3,8,9]. Other studies have shown improved knowledge and adherence to pharmacotherapy [10].

Implications for daily practice

A practical problem that frequently was addressed by the elderly in our home based interviews was dividing tablets. Because of physiological changes elderly have to use lower dosages of some specific medicines, so tablets with dosages suitable for healthy adults have to be divided usually by these elderly patients themselves. Many tablets are too

hard or too fragile to divide, when they break the parts are unevenly divided or multiple parts arise. For as long as lower dosage tablets are not commercially available and elderly have to divide their tablets themselves tablet splitting aids are available, but this still is a second-best option. Another solution for this problem would be preparing capsules in lower dosages, but this is a labour-intensive activity and because of high work-pressure not all pharmacies will be very enthusiastic about making them. The ideal solution for this problem should be the availability of tablets with lower dosages. When this is commercially not very interesting for manufacturers some compensation should be offered by the government to make this activity more interesting for companies.

A number of problems that were identified in our study could be solved by giving extra information and instruction about the use of medicines and their administration devices. A number of tools making the administration of medicines more easy exist (eg. eye drop tools, aerosol aids), but not all patients seem to be are aware of them. Not all administration problems can be solved but probably a number of patients will benefit from these tools. In the pharmacy knowledge about these tools should be present and they should be offered proactively whenever there is a suspicion of problems. In future more emphasis should be given to complex administration forms. The pharmacy assistant can realise this in daily practice by asking the patient about practical problems when dispensing medicines. Furthermore use of complex administration forms and associated problems should be discussed when performing medicine consultations .

As we have seen in our study concerning prescription-related problems, improvements regarding pharmacotherapy can be recommended for almost all elderly patients on polypharmacy. Prescribing for the elderly should be considered more carefully and repeat prescriptions should be monitored more systematically, for example, by means of treatment reviews. Different types of problems and problem categories that are to be expected in the elderly are described in our tool for medication review. When performing medication reviews all problem categories described in this tool should be kept in mind. To get used to this process a medication profile form can be used in which all medicines (vertical axis) and all problems categories (horizontal axis) are shown. For each point of attention a mark can be made in the row of the particular medicine in the column of the particular problem category. This presentation of medicines and problem categories helps to cover all relevant problem categories for each medicine. As copying all medicines on such a form is labour-intensive this process should be computerised. Forms should be printed with all medicines and dosages on it from the pharmacy system.

We recommend performing treatment reviews for elderly patients on polypharmacy, but not all pharmacists may be willing and capable of performing these reviews. Firstly, performing such reviews takes a lot of time, especially in a pharmacy population

comprising many elderly patients. However, most participants in our process evaluation indicated that it should be possible to perform treatment reviews for the elderly population if they were spread over the entire year.

Secondly, we offered participating pharmacists a training session about treatment reviews. In this training problems related to ageing and medicine use and the categories of problems that could be identified were discussed, but there was no time to give an update of complete pharmacotherapy. In the interviews on telephone we asked the pharmacists if they felt capable of performing these reviews and performing case conferences with the GP (defending their own points of attention). All pharmacists indicated that they felt capable, although they needed time to prepare the recommendations regarding the pharmacotherapy of a particular patient. In our study most participating pharmacists were younger pharmacists who had had a good undergraduate education in pharmacotherapy. Furthermore these pharmacists were specifically interested in the subject. Because of the variability in the knowledge of (and interest in) pharmacotherapy between pharmacists in the Netherlands we propose that an adequate training (including pharmacotherapy and prescription guidelines for most common diseases) should be offered in the continuing education program to train pharmacists to become licensed treatment reviewers. Valuable input for these training can be extracted from the composite screening tool that we presented in chapter 4.

In the past the focus of the pharmacist was aimed at preparing medicines in the pharmacy. This focus is nowadays shifted towards pharmacotherapy, while in future the pharmacist should become more patient oriented. This is also proposed in a report of the Dutch Patients' and Consumers' Federation [20]. This report made clear that patients would like to see a community pharmacist to act as a personal adviser on pharmacotherapy, for example, by means of medicine consultations. Although we think that patients can benefit from such a consultation they are not yet performed routinely in Dutch pharmacies[21]. The opportunity to talk about pharmacotherapy with a pharmacist should be more emphasized in the individual pharmacies. A national campaign by the Royal Dutch Pharmaceutical Society (KNMP) may be helpful to communicate this service to a broad public.

To deliver this service adequately, pharmacists should have the skills and interests to perform patient consultations. Additional training should be offered in the continuing education program for pharmacists who need to improve their skills in the area of patient communication. Another problem is the large amount of time that medicine consultations may take. Not all pharmacies are nowadays organised in a way that allows to spend large amounts on these kind of consultations. Probably pharmaceutical consultants (pharmacy assistants with higher vocational education aimed at pharmacotherapy) can contribute and take their share in performing patient consultations. Recently the first group of

pharmaceutical consultants finished their studies, these consultants do have to find their way and tasks in daily practice. Pharmaceutical consultants should have enough knowledge to perform medicine consultations with patients using plain pharmacotherapy, when necessary they can call the pharmacist for help. Medication consultation with patients having complicated pharmacotherapy (patients using higher number of medicines prescribed by different physicians, suffering from a number of different conditions) should be performed by pharmacists.

To diminish user- and prescription-related problems clinical medication reviews can be performed. This involves a complete treatment review (with the GP) supplemented by a patient consultation. Worthwhile patient information concerning actual use and practical problems using prescribed medicines and OTC (over the counter)-medicines can be used. Although we think it should be preferable to perform these clinical medication reviews, no studies considering this subject in the Dutch situation have been published yet. Furthermore, we think that high numbers of Dutch pharmacists have not yet started with the regular performance of treatment reviews. Because the combined form is even more labour-intensive, we think that pharmacists should start performing treatment reviews with the GP, when this becomes common practice patient consultations can be supplemented.

Recommendations for treatment reviews

On the basis of our intervention study, our process evaluation and earlier studies by other research groups, we would like to present the following conclusions and recommendations:

- Performing treatment reviews is effective in reducing the number of prescription related problems [1-3,7].
- It seems recommendable to start the process of treatment review with a pharmacotherapy audit meeting with GPs and pharmacists focusing on special considerations for prescribing in the elderly, polypharmacy and treatment reviews (Chapter 7 Process evaluation).
- In daily practice it will be recommendable to focus the case-conferences on the most complex patients; frequently encountered recommendations can be given in writing or can be talked about shortly (Chapter 7 Process evaluation).
- Treatment reviews should be repeated periodically, firstly, because the effect of the intervention declines after a period of time (Chapter 6 Intervention study). Secondly, because other medicines may be used or conditions can be identified the evaluation has to be repeated periodically. Thirdly, because pharmacotherapeutic guidelines are continuously improving, there can be new points of attention for patients with the same medicines. And lastly, because there will always be new elderly patients who qualify for a treatment review.

- Treatment reviews with the GP should ideally be accompanied by consultations with the patient (chapter 4). Patients also have worthwhile information about their knowledge and actual use of prescribed medicines and OTC (over the counter)-medicines. By means of patient consultations knowledge and motivation for use of their medicines can be optimised [3,8-10].

Responsibilities of health care professionals

Different health care professionals working with medicines can help to prevent drug-related problems in the elderly by performing different activities. In textbox 1 some examples of such activities are shown.

Extra attention should be given to each first prescription of a new medicine, clear information should be given by the prescriber (why using this medicine, how to use this medicine, is this medicine for incidental or chronic use, are there side effects to be expected etc.). In the pharmacy basically the same information should be repeated. When a medicine is intended for chronic use attention should be given to the second time a medicine is dispensed at the pharmacy. At this time the patient has some experience with the use of this particular medicine and will be more interested in extra information and probably does have some questions about the medicine.

Problems can emerge when repeat prescriptions are continued without proper monitoring[22]. Treatment reviews can help physicians to reassess periodically whether repeat prescriptions are still necessary and whether dosages still are suitable for the particular patient. Furthermore they can help to ensure that regular checks to monitor the effectiveness and safety of repeat prescription are performed (e.g. by measuring blood pressure, potassium level etc.).

Moments with a high risk of drug-related problems are hospital admission and discharge. In most hospitals a pharmaceutical transfer-point is active. Pharmacy assistants working at these transfer points are in most instances responsible for identifying current medicine use for patients being admitted to the hospital and furthermore they also play a key role in the communication about discharge prescriptions.

The responsibilities of different health-care professionals concerning medication safety should be described in a National Primary care Collaboration Agreement (Landelijke Eerstelijns Samenwerkings Afspraak = LESA). In such a document all points of attention considering this particular subject are highlighted. In local settings (e.g. pharmacotherapy audit meetings) agreement should be reached considering the responsibilities and practical performance of the tasks related to this subject.

Textbox 1 Responsibilities of different health care professionals in primary care considering medication safety in the elderly

Health care professional	Activity	Activity aimed at diminishing
Pharmacy assistant	Check for problems associated with practical use of medicines	User related problems
	Synchronise repeat prescriptions	User related problems
	Offer administration aids when necessary	User related problems
	Provide extra information in case of a first or second prescription	User related problems
	Assisting in performing medication surveillance	Prescription related problems
Pharmacy assistants at pharmacy transfer point in hospital	Improving communication between community pharmacy and hospital pharmacy at hospital admission and discharge	User and prescription related problems
Pharmaceutical consultant	Perform patient consultations (for patients on plain pharmacotherapy)	User and prescription related problems
Community pharmacist	Medication surveillance	Prescription related problems
	Perform patient consultations	User and prescription related problems
	Perform treatment reviews	Prescription related problems
GP assistant	Be alert when elderly indicate having problems with practical use of medicines	User related problems
	Assisting monitoring repeat prescriptions (perform regular checks when necessary)	Prescription related problems
Practice nurses	Provide information when prescribing a medicine for the first time	User related problems
	Monitor repeat prescriptions for their specific area of treatment (perform regular checks when necessary)	Prescription related problems
General practitioner	Provide information when prescribing a medicine for the first time	User related problems
	Perform treatment reviews	Prescription related problems
	Monitor repeat prescriptions (perform regular checks when necessary)	Prescription related problems
	Discussing need for repeat prescription	Prescription related problems

Nowadays more and more outpatient pharmacies at hospitals are opening and they dispense medicines to patients who are being discharged. Furthermore, special pharmacies for night and weekend hours are opening, they provide medicines and pharmacy services to the patients after closing hours of their regular community pharmacy. A recent development is the dispensing of some specialist medicines by only one pharmacy in the Netherlands. It is critical to have good communication between these types of pharmacies and the community pharmacy of the particular patient about the medicines being delivered and about dosage changes in medicines already used. In most areas communication is realised by means of computer networks or computerised messages in a secured system, but in other instances, especially when communication is necessary beyond a certain region, communication is arranged by means of fax or postal messages. This is a second-best solution because messages can get lost and hence medication surveillance can become

suboptimal. Probably such problems will be solved when the nationwide computerised pharmaceutical register is implemented [30], but until then community pharmacists should take the responsibility to keep the pharmaceutical register of their patients up to date. Medicines not delivered in the own pharmacy should be entered in the pharmaceutical register to maintain medication safety. On the other hand, when dispensing medicines to a patient not registered in a particular pharmacy this should be communicated to the community pharmacy in which the patient is registered (with consent of the patient). The patient also has his own responsibility, of course, in this respect. When the patient orders medicines on the internet and gives no complete information about his medical and/or pharmaceutical record no optimal medication surveillance can be performed. This is also the case when patients do not give consent to send a message to their own pharmacy.

Policy implications

In the Netherlands, as well as in other European countries, the population is ageing. When people are getting older they suffer from more diseases for which medicines should be used. This high number of medicines used by the elderly is responsible for high expenses. Because of deterioration of body functions (e.g. liver and kidney) elderly are more prone to drug-related problems. Side effects, drug-disease and drug-drug interactions and hospitalisation caused by use (or non-use) of medicines are responsible for healthcare problems associated with even higher expenses. Consequently, pharmacotherapy for people using high numbers of medicines, especially for the elderly, should be monitored extensively. This can be done by means of regular treatment review. A small minority of 5-15% of the health-care professionals included in our study felt that a financial fee would be needed to compensate for the additional time spent on performing treatment reviews. It seems that the majority of GPs and pharmacists included in our study found it a self-evident part of their professional quality standards, but we do not know whether this is a proper representation of all GPs and pharmacists in the Netherlands. Treatment reviews are still an extra service in The Netherlands that is not yet part of routine practice everywhere. Rewarding the performance of treatment reviews within the upcoming new rewarding system for pharmacists may encourage health care professionals to take up this activity.

In the Netherlands the role of pharmacists has changed from just dispensing medicines to guiding pharmacotherapy, and this role will further develop towards a patient-centered approach. The community pharmacist has recently been included in the Dutch law on Medical Treatment (“Wet Geneeskundige Behandel Overeenkomst”). According to this new law good pharmacotherapeutic treatment is a shared responsibility of physicians and pharmacists. Performing treatment reviews jointly can be considered as one way to reach this goal. When the pharmacist has this shared responsibility for good pharmacotherapeutic

treatment, different financial fees should be offered for performing quality improvement tasks such as treatment reviews, patient consultations or elaborate information about a medicine when dispensed for the first or second time to a particular patient. A rewarding system that differentiates according to the efforts made, replaces the current fixed financial fee for each prescription that is dispensed independently of the activities related to that dispensing.

Recommendations for further research

Although we decided to focus our research project on the improvement of geriatric prescribing, and hence did not study interventions aimed at user-related problems, we think that the number of user-related problems should decrease as well. To study how both user- and prescription-related problems can be diminished, studies considering clinical medication reviews should be performed. A clinical medication review involves a complete treatment review (with the GP) supplemented by a patient consultation. In clinical medication reviews, medicines are not examined in isolation but considered in context of the patient's condition and the way they live their lives. This means listening to the patient's views and beliefs about their medicines, reaching an honest understanding of their medicine taking behaviour and taking full account of their preferences in any decisions about treatment. Involving patients as partners in such a review will lead to informed agreement about medicine use, leading to better understanding and adherence, this principle is also known as "concordance" and is already being used in other areas of health-care.

When such a study is performed it should include outcome measures at the level of the patients themselves, to measure the clinical consequences in terms of health status, health related patient satisfaction, numbers of falls, functional status, hospital admissions and mortality rates. Such studies should include large populations of the elderly because medication is just one of the parameters that influences these clinical outcome measures. These kinds of studies have already been carried out for home-based interventions after hospital admissions to prevent readmissions [23,24] and variable and unexpected results were seen.

Drug induced hospital admissions are seen frequently and, as we have seen in our introduction, a small number of drug classes is responsible for more than half of these admissions[12,25,26]. A number of researchers have studied risk factors related to these drug-related hospital admissions[27-29]. Further research considering risk factors and risk-models for all kinds of frequently seen drug-related hospital admissions should be performed. When these risk models are known they should be used to identify patients at increased risk of hospitalisation. To implement these risk models in daily practice feasible

implementation programs should be offered. Uptake of risk factors in pharmacy and general practice systems should be preferable (if possible).

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Summary

This thesis is aimed at improving medication safety for the elderly. In our introduction (chapter 1) the rationale of our study is described. We give an impression of the problems associated with ageing of the population and the increasing numbers of medicines used by these elderly. The elderly using multiple medicines will experience problems by the practical use of medicines and probably improvement in pharmacotherapy can be made. Furthermore we focussed on medication reviews, in which complete pharmacotherapy is being screened and points of attention are highlighted.

Part I Problems

In chapter 2 we describe our study in which we wanted to investigate the type, number, and clinical relevance of practical problems using medicines self-reported by home dwelling elderly on polypharmacy. Furthermore this study was aimed at developing a risk-model to identify elderly drug-users at risk of user-related problems.

The study was a cross-sectional study conducted among 286 home dwelling elderly on polypharmacy (≥ 75 years, ≥ 4 medicines) in the Netherlands. The user-related problems found were divided into problem categories and subsequently a pharmacist and a general practitioner classified the problems into those with low and those with (potential) clinical relevance. Factors possibly associated with problems (both for all and relevant problems) were identified, and subsequently tested in multivariate models using logistic regression.

In this study 398 user-related problems were observed in 189 patients (66% of all participants). After classification of user-related problems only 26 % appeared to be of potential clinical relevance (26% of all participants). When including clinical relevance a shift in predominantly present problem categories is observed. Furthermore, the risk model for problems with potential clinical relevance contains more factors than the model which considered all problems. Factors associated with potential clinically relevant problems are emotional or physical problems interfering with social life, communication skills (vision and hearing), using tablets that have to be divided, using inhaled medicines, and the number of medicines used.

Out of this study we concluded that although user-related problems are seen in about two-thirds of the participants, in only one out of four participants the problems were considered to be of potential clinical relevance. With inclusion of clinical relevance, other problem categories become more dominant. A more specific risk model is designed to select elderly patients that are most likely to have problems in need of more urgent intervention.

In chapter 3 we describe our study aimed at determining nature, volume and clinical relevance of prescription-related points of attention in the elderly. This was studied by means of an in depth analysis of pharmacotherapy by a multidisciplinary expert panel consisting of general practitioners, geriatric specialists, clinical pharmacists and community pharmacists. Pharmacotherapy of 102 home-dwelling elderly on polypharmacy ($\geq$ 75 years, using $\geq$ 4 medicines continually) living in the Netherlands was included in this in depth analysis and was studied by means of a two-round consensus method.

We saw that in pharmacotherapy of almost all elderly (98%) prescription-related points of attention could be identified. Points of attention could be identified in prescribed medicines concerning 94% of all elderly, thirty percent of these points of attention were considered to be of direct clinical relevance. In 61% of all patients a medicine could be added to improve pharmacotherapy, 25% of these prescribing omissions were considered to be of direct clinical relevance.

From these results we concluded that the regular performance of treatment reviews should be part of routine in primary care as it yields significant numbers of prescription-related points of attention. Although not all prescription-related points of attention were considered to be of direct clinical relevance, all points of attention do ask for a signal to the prescribing physician.

In chapter 4 we describe a composite screening tool for medication reviews. The regular performance of medication reviews is prominent among the methods that are advocated to reduce the extent and seriousness of drug-related problems, such as adverse drug reactions, drug-disease interactions, drug-drug interactions, drug ineffectiveness and cost-ineffectiveness. Several screening tools have been developed to guide practising healthcare professionals and researchers in reviewing the medication patterns of elderly patients, but each of these tools has its own limitations. In this chapter we describe a wide range of prescription-related, treatment-related and patient-related issues that should be taken into account in the implicit reviewing of medication patterns. A broad selection of concrete examples and references that can be used as basis for the explicit screening of medication patterns in outpatients is also offered.

In chapter 5 we describe our study in which we studied drug-induced hypoglycaemia. In this study we wanted to determine the incidence of drug-induced hypoglycaemia caused by different kinds of blood glucose lowering drugs. Furthermore we tried to identify a risk-model for the occurrence of these drug-induced hypoglycaemia. Hypoglycaemic events were seen in 1 out of 12 patients during the study period. The risk was four times higher in insulin users with or without oral agents (39.11 and 39.04 per 1000 person years respectively) than in users using only oral antidiabetics (9.88 per 1000 person years). In the multivariable analyses use of insulin and renal impairment remained

significant for all users of hypoglycaemic agents (both associated with an increased risk). Use of tolbutamide (associated with a decreased risk) and use of medicines having an influence on CYP2C9 (associated with an increased risk) remained significant for users of sulfonylurea derivatives. Because insulin users are at higher risk for hypoglycaemia than users of oral antidiabetic drugs it seems particularly relevant that elderly insulin users can adequately recognize and rectify upcoming hypoglycaemic events. As the risk of hypoglycaemia is also greater in elderly users of glibenclamid than in users of tolbutamid, the latter sulphonylurea derivative is the drug of choice in this drug class. Finally, more attention should be paid to interactions between sulphonylurea derivatives and CYP2C9 modifying drugs (such as co-trimoxazole).

Part II Improvement of medication safety

In chapter 6 we studied the process of treatment review. We determined which procedure for treatment reviews (case conferences versus written feedback) results in more medication changes, measured at different moments in time. Another goal of this study was to determine the costs and savings related to such an intervention. This was done by means of a cluster controlled trial in primary care. Treatment reviews were performed by 28 pharmacists and 77 general practitioners (GPs) concerning 738 elderly people on polypharmacy (≥ 75 years, ≥ 5 medicines). In one group pharmacist and the GP performed case-conferences on prescription related problems, and in the other group, the pharmacist passed the results of a treatment review on to the GP as written feedback. We counted the medication changes following clinically relevant recommendations and calculated the costs and savings associated with the intervention at various times.

In this intervention study we saw that significantly more medication changes were initiated (42 vs 22, $p = 0.02$) in the case-conference group. This difference is also present 6 months after the treatment reviews (36 vs 19 $p = 0.02$). Nine months after the treatment reviews, the difference lost significance (33 vs 19 $p = 0.07$). Additional costs in the group with case conferences seem to be covered by the slightly greater savings in this group.

Out of this study we concluded that performing treatment reviews with case conferences leads to greater uptake of clinically relevant recommendations. Extra costs seem to be covered by related savings. The effect of the intervention declines over time, so performing treatment reviews for the elderly should be integrated in the routine collaboration between GP's and pharmacists.

In chapter 7 we looked further into the process of treatment reviews, we aimed to describe the feasibility of two methods for treatment review (results were given to the GP either in case-conferences or in written feedback), and to determine if and how the process

of treatment review can be improved. This was studied by means of written questionnaires, structured telephone interviews, and analysis of various features of the treatment reviews that were recorded during the intervention study.

In this process evaluation we found some differences between both intervention groups. The pharmacists in the case-conference group made more recommendations to the GPs (non significant). Significantly more recommendations were identified by the pharmacists themselves in the case conferences group. Health-care professionals accepted an intervention with personal contact in case conferences better than an intervention with feedback in writing. They were more positive about the process of treatment review presented personally, although there were not always as many medication changes as they had hoped for. They also had concrete suggestions for improving the intervention, such as using a combination of written feedback and case conferences, and reserving the case conferences for the most complex cases. From this process evaluation we concluded that treatment reviews for the elderly in primary care are feasible, although improvements in the process for treatment review can be made.

Chapter 8 concludes this thesis. In this chapter the findings and considerations regarding the studies as performed for this thesis are discussed. From our studies we can conclude that the elderly are suffering from user- and prescription-related pharmaceutical care problems. Furthermore, we saw that performing treatment review leads to a decrease in the number of prescription-related problems. Because of positive findings in our studies we recommend performing treatment reviews for the elderly in primary care. For patients with complex pharmacotherapy feedback should be given in case-conferences, for less complex patients feedback can probably be given in writing.

Because user-related problems were also seen frequently we think that treatment reviews ideally should be supplemented by a medicine consultation with the patient (clinical medication review). Because the combined form is even more labour-intensive, we think that pharmacists should start performing treatment reviews with the GP, when this becomes common practice patient consultations can be supplemented.

Because no studies regarding clinical medication review in the Dutch primary care system are performed yet, we recommend to study the effectiveness of these reviews. In such a study outcome measures at the level of the patients themselves should be measured.