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General introduction
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The word pharmakia (φαρμακεία), of which we derived the words pharmacy, pharmacist, and pharmaceutical, means in ancient Greek both the use of medication and poisoning.

Medication review may be a useful intervention in reducing inappropriate medication use, thereby reducing geriatric problems and improving quality of life. The objective of this thesis is first to investigate the effectiveness and implementation fidelity of an optimized medication review intervention in older people with geriatric problems in general practice and second to gain more insight into the types and effects of patient participation in medication reviews.

In this chapter the problem of inappropriate medication use, and the group of vulnerable older people and geriatric problems are described. The challenges and knowledge gaps within the field of medication reviews on the effectiveness, the best target group, patient participation and implementation issues are outlined. Finally, the aims and outline of each chapter of this thesis are explained.

Background

Increasing number of older people

The world population is aging, due to increased life expectancy and declined birth rate. Almost all countries are experiencing growth in the number and proportion of older persons in their populations. The number of people aged 80 years or over is increasing too; the global population aged 80 years or over is projected to grow from 125 million in 2015 to 202 million in 2030 and to 434 million in 2050.¹ In The Netherlands the prospects are that the number of older persons above 65 years will increase from 2.7 million in 2012 to 4.7 million in 2041, corresponding to an increase in proportion of the total population from 16% to 26%. In 2040, one third of all older adults above 65 years will be aged 80 years and older.² The rising number of older persons leads to an enormous...
pressure on healthcare systems and costs because of chronic diseases and medication use.

**Multimorbidity and medication use**
Multimorbidity, defined as two or more chronic diseases is more common at higher age and is associated with reduced functional status, and increased use of health care and high mortality. Estimates of the prevalence of multimorbidity vary widely due to different definitions, settings and sources, and range from 13-72%.\(^3\)\(^5\) The management of multiple chronic diseases poses many challenges, amongst others due to conflicting treatment guidelines and the use of multiple medications.\(^6\) The use of multiple medications is often referred to as polypharmacy, the simultaneous use of several medications which is often defined as the concomitant use of four or five or more chronic medications.

The prevalence of polypharmacy is around 30% in people over 65 years and older in both Europe and the US.\(^7\)\(^9\) Polypharmacy prevalence numbers rise significantly with age. In the Netherlands in 2015, 13% of the general population uses five or more medications, this percentage rises to 25% for people between 65 and 75, 33% for people between 70-75 years and 45% for people over 75 years.\(^9\) Despite increasing attention for polypharmacy in older people, it is still increasing. This is partially explained by aging, but also due to the increase of medication use and the development and implementation of guidelines.\(^7\)\(^9\) Polypharmacy in itself does not always pose a problem, a more accurate term to use when discussing the problems and challenges involving the use of multiple medications is “inappropriate polypharmacy”. Polypharmacy is associated with adherence problems, an increased risk for and potentially inappropriate prescribing and medication use, including underprescribing, adverse drug reactions, unplanned hospital admissions, and mortality.\(^10\)\(^12\)

**Inappropriate prescribing and inappropriate medication use**
Inappropriate medication may be related to prescriber-related factors (inappropriate prescription) and patients related factors (inappropriate medication use). Prescriber related factors include e.g. medically non-indicated medication or inappropriate dosage. Patient-related factors include e.g.
(perceived) ineffectiveness of drugs, adverse effects, lack of knowledge, user problems, and non-adherence problems. In addition, the organization of the healthcare system also contributes to inappropriate medication. This includes lack of knowledge or training on pharmacotherapy for older people among prescribers and dispensers. There may be barriers in communication and exchange of medical and medication files between different prescribers and pharmacists. In primary care, guidelines and limited consultation time often only allows to cover one or two complaints instead of the overall health and medication status and there is not always agreement on the primary responsible physician for the overview on the medication of the older person when multiple prescribers are involved.

International data suggests that one in five medication prescriptions for community-dwelling older adults is inappropriate. Inappropriate medications for older people are defined by the American Beers Criteria Expert Panel as "medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available". Inappropriate prescribing is a major public health problem and a common cause of adverse drug events, drug-drug and drug-disease interactions in older people resulting in morbidity, high health care costs and mortality. Inappropriate prescribing is associated with the female sex, advanced age and the number of medications prescribed. A broadly studied topic are medication-related hospital admissions. In the Netherlands, the HARM study in 2008 showed that about 6% of the unplanned hospital admissions were medication related and almost half was potentially preventable. A recent report on medication safety in The Netherlands showed that the absolute number of medication related potentially preventable hospital admission is still increasing. Determinants of preventable hospital admissions were impaired cognition, 4 or more comorbidities, dependent living situation, impaired renal function, non-adherence to medication and polypharmacy.

One of the reasons for inappropriate medication use in older people is that pharmacokinetics and pharmacodynamics of many medications are altered with age. Relevant pharmacokinetic age-related changes are a reduction in first-pass metabolism, increased bioavailability, changes in the drug distribution of the body due to changes in body composition, protein
binding, and drug clearance of the liver and kidney. Some important age-related changes in pharmacodynamic responses are sedation and extrapyramidal symptoms for antipsychotics, bronchodilation for beta-agonists, antihypertensive effects for beta-blocking agents and verapamil, anticoagulant effects for vitamin K antagonists and a peak diuretic response for furosemide use. Variability in responses to medications are larger with advanced age, e.g. with antipsychotics.19

Inappropriate prescribing can be divided in underprescribing, misprescribing and overprescribing. Explicit and implicit criteria are used to assess the (in)appropriateness of medication. Explicit criteria are medication list based tools such as the Beers criteria or START (Screening Tool to Alert doctors to Right Treatment) and STOPP (Screening Tool of Older Person’s Prescriptions) criteria, based on expert opinions and evidence form the literature.20,21 Explicit criteria are lists to screen for inappropriate prescribing, medications to be avoided by older people and some lists also assess underprescribing, potentially prescribing omissions. Explicit methods require little clinical insight and can sometimes be applied to existing datasets. Implicit methods involve a clinician’s judgment of appropriateness for the individual patient based on the medical history and patients’ information.

In addition, to inappropriate prescribing, a variety of other problems with the use of inappropriate medication may interfere with the effectiveness and safety of effective pharmacotherapy. Examples of these problems are difficulties with adherence or compliance with the medication as prescribed by the patient, patient knowledge, monitoring or administration problems.

**Drug related problems**

Interventions to reduce inappropriate prescribing and medication use often aim to reduce potential drug related problems (DRPs). DRPs differ from inappropriate prescribing in their possibility to potentially affect health outcomes. According to the Pharmaceutical Care Network Europe (PCNE) a Drug Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.22 Inappropriate medication use by the patient such as adherence problems or user problems,
but also dosing or monitoring problems can all be drug related problems. DRPs are also called Medication Related Problems or Pharmaceutical Care Issues. There are different classification systems for DRPs, there is no uniformity on this subject. Classification can be relevant to document the DRPs in daily clinical practice, but also for research. Examples of these systems are the PCNE classification system, the system described by Hepler and Strand and DOCUMENT.23-25 There are differences between these systems in terms of validity, hierarchical problem classification, number of categories and distinguishing between problems and causes. However, all systems use more or less the following main categories: drug selection problem, undertreatment, adverse reaction, dosage problems, adherence problems. The systems differ with respect to the inclusion of DRPs as monitoring problems, practical problems, education problems and treatment costs.

Inappropriate medication and geriatric problems

Bernard Isaacs was the first to use the term geriatric giants. He suggested that the clinical presentation of problems by older patients was dominated by the giants of geriatrics: immobility, instability, incontinence and intellectual impairment. They have in common multiple causation, chronic course, deprivation of independence and no simple cure.26 The atypical (non-specific or silent) disease presentation is common in the older patient and a marker for frailty and predictive of poor hospital outcomes.27 The term giant refers to the major burden of these functional impairments of daily living but also to the high prevalence among older people.

Inappropriate medication may increase the risk of the occurrence and persistence of geriatric giants. The symptoms of geriatric giants are among the most common adverse drug reactions. The relation between inappropriate medication and geriatric giants is for some problems better studied than for others and the causal pathway, the extent and order of the precise associations are complex. Most studies focused on the association between polypharmacy and geriatric giants.

For immobility it has been suggested that a higher number of medications used mediates the excess adverse drug events risk observed with
increasing mobility limitation. The use of benzodiazepines and anticholinergics is associated with functional status decline, of which mobility is an important component. Its relation with suboptimal prescribing in general gave mixed results. Inappropriate pain management and muscle pain or fatigue due to e.g. the use of statins may also limit mobility.

For instability, falls and medication use are studied most frequently. A large meta-analysis with mainly observational studies concluded that the use of sedatives, hypnotics, anti-depressants and benzodiazepines demonstrated a significant association with falls in older people. These types of drugs are often considered inappropriate for elderly. Studies on the withdrawal of fall-risk increasing drugs, including cardiovascular and psychotropic drugs, seem to be effective interventions for lowering the incidence of falls. In the STOPP criteria, there is also a separate section of medications related to elevated fall risk and there are lists with fall-risk increasing drugs for older people. The relation between dizziness and inappropriate medication is somewhat less clear, however polypharmacy was found to be predictive of and associated with dizziness.

Urinary incontinence is also associated with polypharmacy. In a longitudinal study polypharmacy was associated with an increased risk of lower urinary tract symptoms (LUTS) in women above 70 years. Several medications, such as alpha-blockers and estrogens, are associated with urinary incontinence and have an impact on the lower urinary tract. Moreover, when treating LUTS in older patients, with polypharmacy and comorbidities, the increased potential for drug-drug interactions should be considered.

Several potentially inappropriate medications may impair cognition. In a prospective study sedative hypnotic agents, especially long-acting benzodiazepines, frequently caused cognitive impairment in an older population. The Beers and STOPP criteria mention for amongst others certain anticholinergics, benzodiazepines, opiates, and antipsychotics to avoid these medications in demented or cognitively impaired older people. Older people are particularly vulnerable to the more subtle cognitive effects (e.g., attention and memory deficits) of drugs with anticholinergic properties and more sensitive to adverse effects of antipsychotics. The relative odd for adverse drug reactions associated with cognitive impairment increases with the number of prescribed drugs, exceeding to 9.0 for patients taking four or more

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prescribed drugs.\textsuperscript{39} In addition, impaired cognition is mentioned as one of the risk factors for medication related hospital admissions in a large prospective Dutch study.\textsuperscript{18}

Many older people have two or more of these geriatric giants at the same time. In the nineties, Tinetti et al. already looked into the shared risk factors for incontinence, falls and functional dependence in an attempt to unify the approach to geriatric giants. Polypharmacy was associated with each of the geriatric syndromes and functional decline.\textsuperscript{42} All geriatric giants are multifactorial, however medication use is probably one of the most modifiable or most easiest modifiable risk factor.\textsuperscript{43} In this thesis, we refer to the geriatric giants as geriatric problems. In recent years other ‘giants’ are added to the original four I’s of Isaacs, such as impaired vision and hearing loss, these are not discussed in this thesis as they have less relations with inappropriate medication.

Medication reviews

\textit{Definition and objectives}

Medication reviews are one of the interventions that aim to reduce inappropriate prescribing and medication use. A medication review is defined by the UK Task Force on Medicines Partnership as a “structured, critical examination of the patient’s medication with the objective of reaching an agreement with the patient about treatment, optimising the impact of medications, minimizing the number of drug related problems (DRPs) and reducing waste”.\textsuperscript{44} This definition is also used for this thesis. In 2008 three types of medication reviews are described by the National Prescribing Centre and the NHS in the UK.\textsuperscript{45}:

- Type I; The prescription review addresses technical issues relating to the prescription or medication, the patient does not need to be present, nor access to patient’s full notes.
- Type II; The concordance and compliance review addresses issues relating to the patient’s medication taking behaviour, patients are usually present.
Type III. A Clinical Medication Review (CMR) addresses issues relating to the patient’s use of medication in the context of their clinical condition and requires patients to be present.\textsuperscript{45}

The different medication review services currently being implemented in different countries have mostly similar objectives, but with different intensity, definitions, and tools. A lot of countries have their own clinical guideline and name. Examples of these services are medication therapy management (MTM) in the USA\textsuperscript{46}, medicines use review (MUR) or clinical medication reviews in the UK \textsuperscript{45,47}, home medication review (HMR) in Australia \textsuperscript{48}, Comprehensive Medication Reviews in Finland \textsuperscript{49}, Lund Integrated Medicines Management (LIMM) model in Sweden \textsuperscript{50}, and medication reviews (MBO) in The Netherlands \textsuperscript{51}. There are differences between countries or regions in intensity and tools used, which mainly depend on the organization of the health care system; however the purpose of medication reviews are often similar. In most countries, medication reviews are conducted and/or initiated by pharmacists. A survey among European countries revealed that the majority of the European countries only perform type I and II reviews.\textsuperscript{52}

\textit{Medication reviews in the Netherlands}

In 2012, a multidisciplinary guideline was published in the Netherlands for the ‘treatment’ of polypharmacy in older people.\textsuperscript{51} Clinical Medication Reviews using the stepwise approach of the Systematic Tool to Reduce Inappropriate Prescribing (STRIP) are outlined in this guideline. This is a combination of using the implicit START and STOPP criteria (Dutch translation) and explicit criteria following a stepwise approach:

\begin{itemize}
  \item Step 0: Preparation and patient selection
  \item Step 1: Pharmacotherapeutic history
  \item Step 2: Pharmacotherapeutic analysis
  \item Step 3: Consultation between GP and pharmacist and drafting of the pharmacotherapeutic treatment plan
  \item Step 4: Feedback to the patient and determine the pharmacotherapeutic treatment plan
\end{itemize}

The target group for this guideline is defined as older people above 65 years using five or more chronic prescribed medications with one or more of the following risk factors:
• Diminished renal function
• Impaired cognition
• Elevated fall risk
• Signals of compliance or adherence problems
• Not living independently

In addition to this guideline, in July 2015 the Health Care Inspectorate of The Netherlands (IGZ) did come up with new standards for medication reviews and directives for implementation. These included:

1. Agreements on cooperation between prescribers and pharmacists should be documented.
2. Prescribers and pharmacists should conduct medication reviews that follow the inclusion criteria as described in the multidisciplinary guide ‘Polypharmacy for elderly. At least all patients of 75 years and older, using 7 or more medications and have renal failure [(eGFR < 50 ml/min/1.73 m²] should receive a medication review.
3. Healthcare providers should conduct medication reviews in a systematically and measurable manner.
4. Healthcare providers should conduct a minimum number of medication reviews based on a pre-defined growth-model for 2015-2017. In 2017, a pharmacist should conduct medication reviews for at least 100 patients and a GP for at least 25 patients.

In the Netherlands, GPs and pharmacists are the most designated healthcare providers to conduct medication reviews for community-dwelling older people for several reasons. First, non-institutionalised Dutch inhabitants are obligatory listed at a general practice and most patients are registered with one community pharmacy. Second, in general the GP has the most complete overview of the medications used and morbidities compared to other healthcare providers. Third, repeat prescriptions from most prescribers are arranged by the patients’ own GP and pharmacist. Finally, most GPs and pharmacists are participating and organized within regularly pharmacotherapeutic consultation groups.
Challenges and knowledge gaps

Effectiveness of medication reviews

The effectiveness of medication reviews and other pharmacotherapeutic interventions to improve inappropriate medication is a widely studied topic. This is reflected by the large number of Cochrane reviews, systematic literature reviews and meta-analyses published in the last decade. Different settings (primary care, hospitalised or institutionalised patients), for specific or broader subgroups such as community-dwelling elderly, cardiovascular patients, or specific types of medication review were studied. Clinical outcomes measures included quality of life, hospital admission or mortality or population specific morbidity outcomes. Other more indirect outcome measures are prescribing appropriateness measures, DRPs, number of drugs used, adherence, patient knowledge, patient satisfaction, and costs.

The evidence for medication reviews to reduce inappropriate medication use is moderate. There are many different outcome measures for inappropriate medication, such as the Medication Appropriateness Index (MAI), number of drug-related problems, STOPP/START criteria, Beers criteria and many more. Moreover, there is also a large variety in type of interventions, clinical medication reviews or more general interventions to reduce inappropriate medication use or prescribing. This made pooling of results often very difficult. Several recent and less recent systematic literature reviews report that a range of interventions demonstrated improvements in appropriate polypharmacy or reducing potentially inappropriate prescribing, and drug related problems. However, there was a wide range of effect sizes reported and the quality of evidence was rated as low (GRADE).

Evidence on the effectiveness in terms of health outcomes such as improved quality of life, reduced hospital admission rates or mortality is still minimal, inconclusive or lacking. Here again, pooling was not possible due to the large heterogeneity in type of interventions, populations and outcome measures. The evidence on costs of healthcare use and medications and cost-effectiveness of medication reviews is also mixed and of low quality. It seems that there is a lack of robust evidence demonstrating clinical effectiveness and cost-effectiveness of medication reviews compared with
usual care. This thesis focuses on the effectiveness and cost-effectiveness of medication reviews on quality of life and on geriatric problems.

**Target group for medication reviews**

There is no consensus on the best target group for medication reviews. Most guidelines and research focused on polypharmacy patients, with or without additional risk factors. The health care setting, primary care, hospital care, hospital discharged or institutionalized care, also vary. The question is which patients benefit the most, or possibly which target group is most feasible to conduct a review for, or even which target group for medication reviews is most cost-efficient for society. A Dutch case study advocates to pay attention to patients that fall outside the current selection criteria for medication review, but also may have a valid indication for a medication review, such as patients without polypharmacy but with undertreatment or geriatric problems such as falling and dizziness. The authors also state that the current selection criteria for medication reviews in The Netherlands are based on limited available evidence and expert opinions.69

In this thesis, a relatively new target group is studied. We focus on older patients presenting with a new geriatric problem to their general practitioner, instead of e.g. the number of medications used.

**Patient participation**

As described in several guidelines and within the definition of a clinical medication review, patient participation is an essential element of a clinical medication review.

Patient participation is a difficult concept with no clear definition. The model and definition of Thompson70 is used in this thesis. Participation is seen as being co-determined by patients and professionals and occurring only through the reciprocal relationships of dialogue and shared decision making. Thompson et al. 2007 defined levels of patient involvement from the patient perspective. According to Thompson the main distinguishing feature between patient involvement and patient participation is the degree of decision making.70 Not everyone wants to be involved on the same level, some patients prefer the physician to make health care decisions (professional-determined involvement) and others want to take a fully active role (patient-determined involvement).
involvement) or somewhere in between. Moreover, the same patient may wish to be involved at different levels in different circumstances.

For a medication review, the identification of certain DRPs, such as adherence and user or medication knowledge problems can only be identified by the patient. In addition, the actual medication use as indicated by the patient can differ from what is known in the pharmacy and/or with the physician. These discrepancies are known to be larger in outpatients taking a higher mean number of drugs and in people in whom multiple prescribing physicians next to the GP are involved.\textsuperscript{71} The input from the patient about their preferences and medication use, including information of any use of over the counter medication is therefore essential. Involving patients in medication reviews increases the number of identified DRPs, and it seems that these DRPs are assigned a higher priority and have a better implementation rate.\textsuperscript{72}

However, patient participation is very time-consuming. The care is also complex because the patient involvement concerns multimorbidity patients and several different medication guidelines for specific conditions for each patient. For physicians it is very difficult to deal with sometimes seemingly contradictory evidence of the harms and benefits of following disease specific guidelines, and even more to explain this to patients. A qualitative study cited concerns among primary caregivers about patients' and families' inaccurate understanding of harms and benefits of their medication use.\textsuperscript{73} This means for the patient that there is no easy choice between for example two treatment options, but a scala of factors and interactions has to be taken into account.

In this thesis we aimed to provide more insight into the types and effects of patient participation in medication reviews. In addition, patient participation in medication reviews by means of completing a questionnaire has been investigated.

\textbf{Implementation issues}

In The Netherlands, the Dutch guideline for polypharmacy for older people was published in 2012, however since then, its implementation in primary care has had some difficulties.\textsuperscript{74} An evaluation report by Dutch Organization for Health Research and Development (ZonMw)\textsuperscript{75} concluded that important barriers for performing medication reviews in daily practice were patient selection, the working procedure of the medication analysis, assuring continuity of the
process, medication initiated by medical specialists and the considerable time-investment. The limited options for recording in the current electronic patient records of both GPs and pharmacists hinders the patient selection, assuring the continuity of the process and recording and exchange of data and agreements between GPs and pharmacists. Responsibilities were not always clear to all key players.

Also in other countries, the organization and implementation of CMRs are difficult and time consuming. Due to the limited access to medical information for pharmacists, performing full clinical medication reviews including the patient’s information is in many countries still limited.

In this thesis we investigated a medication review method that we hypothesized to be more feasible and to overcome some of these implementation issues. This method may be less time consuming, by streamlining the patient-selection, involving practice nurses and make use of external expert teams.

**Pilot studies**

In preparation of the studies described in this thesis, two pilot care innovation projects on medication reviews in polypharmacy patients in 2009 and 2011 were performed in respectively 14 and 4 general practices of the Academic Network for General Practitioners of the VU University Medical Center in Amsterdam. The first pilot revealed that the time-investment for GPs, pharmacotherapeutic knowledge and organization of the process were barriers for implementation in routine care. In the second pilot project, a patient questionnaire on DRPs was used to reduce the number of contacts with the patient. Streamlining of the medication review process, the use of a patient questionnaire and the use of a dedicated team was deemed suitable for routine care.
Research questions and outline of this thesis

Based on the identified gaps in the literature and experiences from daily practice we formulated the following questions for this thesis:

1. What is known in the literature about ways of patients participation in the medication review process and its effects on the outcomes of a medication review?
2. Can patient participation in medication reviews be achieved via a questionnaire instead of an interview?
3. What is the (cost)-effectiveness of an optimized clinical medication review on quality of life and geriatric problems in comparison with usual care, in older patients with geriatric problems presented in general practice?
4. What is the implementation fidelity of optimized clinical medication reviews in the setting of general practice?

Patient participation was addressed by a systematic literature study and an empirical study comparing personal interviews with a questionnaire. To study the effectiveness and cost-effectiveness of clinical medication reviews we conducted a cluster randomised controlled trial with 518 patients from 22 general practices (the Opti-Med study). An overview of the methods used per research question is presented in table 1.1.
Table 1.1 Overview of the methods used per research question

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Chapter 2 is a systematic literature review on patient participation in medication reviews. As preparation for the RCT a questionnaire was developed and evaluated. Chapter 3 presents the results of an agreement study between the questionnaire and an interview on patient information on medication use and drug-related problems in older patients. Chapter 4 describes the protocol of the Opti-Med study. Chapter 5 presents the results on the effectiveness of the Opti-Med intervention on quality of life and geriatric problems. Chapter 6 presents the results on the cost-effectiveness of the Opti-Med intervention. Chapter 7 shows the results of the process-evaluation of Opti-Med, describing the implementation fidelity of such an intervention. Chapter 8 discusses the main findings of this thesis and recommendations for future research and daily primary care practice.
Chapter 1

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Chapter 8

discusses the main findings of this thesis and recommendations for future research and daily primary care practice.

References

7. Slone Epidemiology Center at Boston University; Slone Survey: Patterns of medication use in the United States. 2006.

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Patient participation in medication reviews is desirable but not evidence-based: a systematic literature review

Floor Willeboordse, Jacqueline G. Hugtenburg, François G. Schellevis, Petra J.M. Elders