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Development and Application of Comprehensive Medication Review Procedure to Community-Dwelling Elderly

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ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Pharmacy, University of Helsinki, for public examination in Auditorium 2041, Biocenter 2, Viikinkaari 5, University of Helsinki, on 30th March 2012, at 12 noon.

Helsinki 2012

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ISBN 978-952-10-7697-8 (pbk.)
ISBN 978-952-10-7698-5 (PDF)
ISSN 1799-7372

Helsinki University Printing House
Helsinki, Finland 2012

Abstract

Populations in Western countries are ageing. At the same time, use of medications is increasing among older people. Age-related changes in the body make the elderly vulnerable to adverse drug events. Thus, ensuring medication safety among this patient group is a growing health care concern. For this purpose, several criteria to indicate inappropriate prescribing among the aged have been developed. Also, different types of medication review procedures have been created in several countries to identify drug-related problems (DRPs).

The aim of this study was to develop a collaborative Comprehensive Medication Review (CMR) procedure applicable to the Finnish health care system and evaluate its usefulness as a means to improve the appropriateness of pharmacotherapy among community-dwelling elderly. The specific aims were 1) to determine the prevalence of potentially inappropriate medication use according to the Beers 2003 criteria among Finnish non-institutionalized population aged ≥65 years; 2) to describe the development and assess participant satisfaction on the CMR accreditation training; 3) to describe the development of the CMR procedure and related documentation, and to assess CMR training participants' satisfaction on the documentation; and 4) to assess the DRPs pharmacists report to collaborating physicians during CMR and the resulting interventions among outpatients aged ≥65 years.

This study applied both quantitative and qualitative methods. The prevalence of potentially inappropriate drug use according to the Beers criteria was studied by using the drug reimbursement register of the Finnish Social Insurance Institution covering the entire non-institutionalized population aged ≥65 years in 2007 (n=841 509, Study I). The development of the CMR procedure and accreditation training involved a review of literature and medication review procedures used in other countries as well as pilot testing by 26 experienced pharmacists undergoing the CMR training in 2005–2006 (Studies II, III). Participants' satisfaction on the CMR training (n=38) and documentation (n=27) were assessed by surveys completed by pharmacists attending CMR training in 2006–2007 (Studies II, III). The DRPs identified and reported to the collaborating physicians during CMR were studied by a retrospective review of CMR case reports (n=121) by 26 community pharmacists attending the CMR training in 2006–2007 (Study IV).

Approximately 15% of the entire non-institutionalized population aged ≥65 years used potentially inappropriate medications in Finland in 2007. This prevalence is low compared to studies in other countries. The most worrying finding was the common use of benzodiazepines: one third of the potentially inappropriate drug use involved these drugs, particularly high-dose temazepam. The 1.5-year CMR accreditation training for practicing pharmacists combines distance learning and face-to-face learning and consists of 5 modules: 1) Multidisciplinary Collaboration; 2) Clinical Pharmacy and Pharmacotherapy; 3) Rational Pharmacotherapy; 4) CMR Tools; and 5) Optional Studies. The participating pharmacists' satisfaction with the training was high but several factors prevent them from conducting CMRs after the training. The collaborative CMR procedure involves access to clinical patient information, home visit with patient interview, a case conference with the collaborating physician and extensive documentation to support the process. The procedure covers four main dimensions critical for safe and appropriate pharmacotherapy for the aged: Aging and Safety; Co-Morbidities; Polypharmacy; and Adherence. When using the CMR procedure, pharmacists reported to collaborative physicians an average of 6.5 DRPs per patient. Most common DRPs were inappropriate drug selection, especially involving psychotropic drugs, and undertreatment. Also treatment of pain was often found to need improvement. Approximately half of the pharmacists' recommendations led to medication changes, i.e., to an average of 3 changes/patient. The most common agreed change was to stop hypnotics or sedatives.

The results of this study confirm many well-known problems in elderly pharmacotherapy: prescribing of inappropriate drugs, undertreatment, and issues related to inadequate management of pain. The CMR procedure could be beneficial for improving pharmacotherapy among older outpatients as a large portion of DRPs identified by pharmacists led to medication changes. Actions to facilitate implementation of the model to Finnish health care system are needed. Also, further studies are needed to evaluate the effects of CMR on clinical, humanistic and economic outcomes.

Acknowledgements

This study was a long process, starting in 2005. It is amazing how many people have been involved and helped me along the way. I want to warmly thank you all!

First, I want to express my gratitude to my main supervisor, Professor Marja Airaksinen, Head of the Division of Social Pharmacy, who supported me throughout the process. Her outstanding expertise, valuable advice and endless patience were essential for this thesis to be completed. Second, I want to thank my energetic employer, pharmacy owner Eeva Savela, who pushed me to start this study. I am grateful for her continuous support and encouragement. I also want to thank my supervisors Professor Raimo K. Tuominen, Head of the Division of Pharmacology and Toxicology, and Professor Alan Lyles, University of Baltimore, for sharing their expertise and giving valuable comments.

Professor Timothy Chen, University of Sydney, and Dr. Kenneth Shermock, The Johns Hopkins Hospital, are warmly thanked for their pre-examination of this thesis and for giving such encouraging comments. Thomas Fulda, BA, MA, is acknowledged for his enormous work reviewing the language and for giving insightful advice.

The material for this study was acquired from multiple sources and the articles were written in collaboration with numerous co-authors. I especially want to thank the members of the TIPPA Coordination group who developed the CMR training and procedure. My warmest thanks go to training coordinator Lea Tuomainen who made the data collection for studies II-IV possible. In addition, I want to thank Lea for her friendship and incredible way of giving feedback and support during the CMR accreditation training. I also want to express my deepest gratitude to all CMR training participants who took the effort to complete the surveys and to provide the CMR case reports for this study. My excellent MSc students Maarit Dimitrow and Johanna Virolainen are warmly thanked for doing a great job with their Master's theses and helping with related manuscripts.

I am grateful for all colleagues and peers who were involved in this process. This concerns foremost Anna Westerling, a recent PhD and a dear friend who was always willing to help and listen. Together we shared the greatest and funniest moments from the first submissions and manuscript acceptances to congresses, but also the surprisingly many moments of despair. Personnel at the Division of Social Pharmacy are all thanked for always being helpful and supportive. PhD student Juha Sinnemäki and PhD Marika Pohjanoksa-Mäntylä are specially acknowledged for their continuous assistance and useful discussions.

The Association of Finnish Pharmacies, The Pharma Industry Finland Research Foundation and The Finnish Pharmacists' Society are acknowledged for their financial support. In addition, the Graduate School in Pharmaceutical Research is acknowledged for providing the 2-year doctoral student position at the University, which enabled full commitment to the PhD studies.

My special thanks go to my dear family, relatives and friends who have always listened, encouraged and shared fun moments to make me forget study-related concerns. I especially want to thank my sisters Saila and Silja, friends Minna, Ralf, Tiina and Topi, and my great co-workers from the Lohja 1st Pharmacy for all hilarious get-togethers and travels. I sincerely thank my mom Seija and dad Erkki for emphasizing the importance of

a proper education to me and my sisters, and for always helping and supporting me. I also want to thank my godparents Juhani and Marjatta for their continuous interest towards my studies.

I own my deepest gratitude to my nearest and dearest ones: my husband Jukka and our wonderful kids Juuso and Jenni. I am thankful for your endless understanding during these years, when I have been always at the computer and often forgetting what is most important in life. Without your support, this would never have been possible. I love you very much!

Lohja, March 2012

Saija Leikola

Contents

List of Original Publications

This thesis is based on the following publications:

I Leikola S, Dimitrow M, Lyles A, Pitkälä K, Airaksinen M. Potentially inappropriate medication use among Finnish non-institutionalized people aged ≥65 years. A register-based, cross-sectional, national study. Drugs Aging 2011;28(3):227-236.[a]

II Leikola SNS, Tuomainen L, Ovaskainen H, Peura S, Sevón-Vilkman N, Tanskanen P, Airaksinen MSA. Continuing education course to attain collaborative comprehensive medication review competencies. Am J Pharm Educ 2009;73(6):Article 108.

III Leikola S, Tuomainen L, Peura S, Laurikainen A, Lyles A, Savela E, Airaksinen M. Comprehensive Medication Review – evidence-base of a collaborative procedure involving pharmacists. (submitted)

IV Leikola SNS, Virolainen J, Tuomainen L, Tuominen RK, Airaksinen MSA. Collaborative comprehensive medication reviews for elderly primary care patients – community pharmacists' findings and recommendations to physicians. J Am Pharm Assoc (accepted for publication June 26, 2011)

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Definitions of the Key Concepts

Adverse drug event
Any injury occurring during the patient's medicine therapy and resulting either from appropriate care or from unsuitable or suboptimal care. Includes adverse drug reactions during normal use of the medicine, and any harm secondary to a medication error, both errors of omission or commission (Council of Europe 2006).

Adverse drug reaction
A response to a medicinal product which is noxious and unintended, and occurs at doses normally used in man (Council of Europe 2006). In such patient responses, individual properties may play an important role (WHO 2000).

Adverse event
An unintended injury caused by medical management rather than by a disease process (Council of Europe 2006). Medication errors are one potential cause of adverse events.

Community-dwelling elderly
In this study, the term community-dwelling elderly is used to refer to persons aged 65 and older not residing in a nursing home or hospital ward. Terms aged/elderly outpatient, ambulatory patient, and primary care patient have been used as synonyms to this term.

Comprehensive medication review
A medication review procedure applied nationally in Finland and requiring accreditation training for pharmacists conducting it. The procedure is based on collaboration between pharmacist and other health care professionals, particularly physicians, and includes access to clinical patient data, a home visit with a patient interview, a comprehensive clinical review of all used medication, case conference with the physician and an extensive documentation to support the process.

Disease management
Patient care services focused on a specific disease, e.g., hypertension, asthma and diabetes, to ensure that population guidelines are followed and to provide patients with the tools and knowledge they need to assume responsibility for their own care (McGivney et al. 2007).

Drug-related problem
Originally defined as "An undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome" (Strand et al. 1990). Currently most often defined as "An event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes" (PCNE 2010). Often used as a synonym with a term "drug-therapy problem" which is defined as "any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with desired health outcomes" (Cipolle et al. 1998, 2004).

Home medicines review
Medication review procedure for home-dwelling people in Australia. Includes patient home-visit, review of all medications and collaboration between an accredited pharmacist and physician (Pharmaceutical Society of Australia 2011).

Medication error
Any deviation from ordinary standards of care appropriate for the time of the medicine therapy of a patient. A non-intentional, preventable omission or failed activity related to the medication use system, which can be the cause of a risk or an adverse event reaching the patient. Medication errors can concern one or several stages of medication use system, e.g., prescription, dispensing, administration, therapeutic monitoring and information (Council of Europe 2006).

Medication review
An evaluation of patient's medicines with the aim of managing the risk and optimizing the outcome of medicine therapy by detecting, solving and preventing drug-related problems (www.pcne.org).

Medication safety
Freedom from accidental injury during the course of medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medicines (Council of Europe 2006).

Medication therapy management
In the United States a service or group of services to eligible patients to ensure that medications are used appropriately, enhance understanding of the appropriate use of medications, increase adherence with prescription medication regimens, reduce the risk for potential adverse drug events, and reduce the need for other costly medical services through better management of medication therapy (Bluml 2005, McGivney et al. 2007).

Pharmaceutical care
The provision of patient-centered practice in which the practitioner assumes responsibility for a patient's medication-related needs and is held accountable for this commitment for the purpose of achieving definite outcomes through designing, implementing, or monitoring a therapeutic plan (Hepler and Strand 1990, Cipolle et al. 2004).

Potentially inappropriate medications
In this thesis, the term potentially inappropriate medications refers to medications that are considered to be inappropriate for persons aged 65 or older because of questionable efficacy, unfavourable benefit-risk or because safer alternatives exist (Fick et al. 2003).

Psycholeptic drug
Medications classified under ATC code N05. These drugs include N05A antipsychotics (i.e., neuroleptics), N05B anxiolytics and N05C hypnotics and sedatives.

Psychotropic drug
Includes above mentioned psycholeptic drugs, and in addition, N06A antidepressants.

Side effect
Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug (WHO 2000). It differs from the term ‘adverse drug effect’, as side effects are not necessarily noxious.

Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
APhA	American Pharmacists Association
ATC	Anatomic Therapeutic Chemical classification
CMR	Comprehensive Medication Review
CMS	Cipolle-Morley-Strand classification for DTPs
CNS	Central Nervous System
DDI	Drug-drug interaction
DMMR	Domiciliary Medication Management Review (Australia)
DRP	Drug-Related Problem
DTP	Drug Therapy Problem
DUR	Drug Utilization Review (USA)
ED	Emergency department
GI	Gastrointestinal
GP	General practitioner
HMR	Home Medicines Review (Australia)
HRQoL	Health-related quality of life
MAI	Medication Appropriateness Index (Hanlon et al. 1992)
MTR	Medication Therapy Review (in MTM)
MMA	Medicare Prescription Drug Improvement and Modernization Act (USA)
MRR	Medication Regimen Review (USA)
MTM	Medication Therapy Management (USA)
MUR	Medicines Use Review (England, Wales)
NACDS	National Association of Chain Drug Stores Foundation (USA)
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
OTC	Over-the-counter
PCNE	Pharmaceutical Care Network Europe
PIM	Potentially Inappropriate Medication
PSA	Pharmaceutical Society of Australia
RCT	Randomized Controlled Trial
RMMR	Residential Medication Management Review (Australia)
SII	Social Insurance Institution of Finland
START	Screening Tool to Alert doctors to Right Treatment (Barry et al. 2007)
STOPP	Screening Tool of Older Person's Prescriptions (Gallagher et al. 2008a)
TIPPA	Tarkoituksenmukainen Informaatio Potilaan Parhaaksi Apteekista; Customized Information for the Benefit of the Patient from the Community Pharmacy (Puumalainen 2005)

1 Introduction

The populations in Western countries are ageing. In Finland, people aged ≥65 years comprised 16.5% of the population at the end of 2007 (Statistics Finland 2011). By 2020 the corresponding percentage is estimated to rise to 23%. Thus, the increasing elderly population with its special needs has become a priority in health care services planning.

Age-related changes in the body (Mangoni 2003, ELDesoky 2007) make the elderly more susceptible to drug-related adverse reactions and hospitalizations (Beijer and de Blaey 2002, Budnitz et al. 2006, van der Hooft et al. 2008a). However, ageing people often have multiple co-morbidities, which leads to increased use of medications. For example in Finland both the overall use of medicines and polypharmacy (>5 medicines) among the aged have increased (Linjakumpu et al. 2002a, Jyrkkä et al. 2006, Jyrkkä 2011). Polypharmacy is an independent risk factor for adverse drug reactions (ADRs) among frail elderly (Hanlon et al. 2006). It can also increase the risk of potentially harmful interactions, especially among the aged (Barat et al. 2000, Bjerrum et al. 2003). Despite the commonness of polypharmacy, undertreatment can also be a significant problem in older people (Ruths et al. 2003, Sloane et al. 2004).

A significant proportion of adverse drug events (ADEs) and ADRs, including those leading to hospitalization, among the elderly are preventable (Beijer and de Blaey 2002, Gurwitz et al. 2003, van der Hooft et al. 2008a). Thus, pharmacotherapeutic decisions for elderly patients should be made with careful consideration and by emphasizing regular monitoring and follow-up. In order to help clinicians make safe medical decisions for their elderly patients, various recommendations and explicit criteria on potentially inappropriate medications (PIMs) and drug-disease combinations have been created in different countries (Kivelä and Räihä 2007, Socialstyrelsen 2003, 2010, Dimitrow et al. 2011). Yet, the use of PIMs continues to be common in many countries, including Finland (Fialova et al. 2005, Hosia-Randell et al. 2008).

Pharmacists have taken action in several countries to be more actively involved in assuring rational pharmacotherapy and medication safety. Different medication review procedures and services have been developed and made available both in inpatient and outpatient settings, e.g., in the Unites States, Australia and UK (Harjivan and Lyles 2002, Fulda et al. 2004, Sorensen et al. 2004, Department of Health 2005, American Pharmacists Association (APhA) and National Association of Chain Drug Stores Foundation (NACDS) 2008, Australian Government 2011a,b). A core idea of these procedures is to recognize, resolve and prevent drug-related problems, DRPs (Hepler and Strand 1990).

In Finland, the Ministry of Social Affairs and Health has placed regular medication reviews and multiprofessional collaboration as key solutions to promote rational pharmacotherapy and to prevent medication-related problems among the aged (The Ministry of Social Affairs and Health 2007). Finnish community pharmacies have taken persistent actions to promote safe use of medicines since the early 1990's. The most remarkable effort has been a national programme in 2000–2003 (TIPPA) where all the key pharmacy stakeholders, including government, universities, continuing education centres and professional organizations united in an effort to improve patient counseling services in community pharmacies (TIPPA Project 2004, Puumalainen 2005, Kansanaho 2006). A

TIPPA follow-up programme in 2004–2007 was built on the findings and experiences of the first phase and focussed on creating more advanced services based on multidisciplinary collaboration. The key service developed under the follow-up programme was the comprehensive medication review (CMR) involving collaboration between pharmacists and physicians, which is the focus of this doctoral thesis.

The literature review of this thesis aims to provide a conceptual, theoretical and contextual framework for the study (Chapters 2–4) The Finnish CMR is based on two international collaborative medication review models, i.e., Home Medicines Review (HMR) in Australia (Sorensen et al. 2004, Pharmaceutical Society of Australia 2011) and Medication Therapy Management (MTM) in the United States (APhA and NACDS 2008). Thus, these procedures and related evaluation studies are described (Chapter 2). As all medication review models basically aim at recognition, prevention and resolving of DRPs, DRP-classification systems and studies on recognition of DRPs by pharmacists during MTM and HMR are reviewed (Chapter 3). Methods to classify PIMs, prevalence of PIM use and association of PIM use with adverse outcomes among the aged are also discussed (Chapter 4). Special focus throughout this thesis is on community-dwelling patients aged 65 and older, from now on referred also as elderly outpatients.

The theoretical framework of this thesis is based on patient-oriented collaborative community pharmacy practice and service development in order to assure safe and appropriate pharmacotherapy with optimum outcomes (Chapter 2). These principles were first introduced in to community pharmacy practice by American scientists Hepler and Strand in 1990 under the concept Pharmaceutical Care (Hepler and Strand 1990). Their landmark article led to worldwide discussion about community pharmacists' contribution to patient care and need for extending their services beyond dispensing. The key idea is to recognize, resolve and prevent drug-related problems.

2 Medication Review as an Implementation of Pharmaceutical Care

2.1 Pharmaceutical Care as Professional Philosophy

The traditional pharmacists' role in health care focused on compounding and dispensing medicines (Berenguer et al. 2004). This role started to expand in the 1960's when clinical pharmacy services evolved in US hospitals (Berenguer et al. 2004). Through the development of clinical pharmacy services pharmacists started to take greater responsibility for patient care and optimization of drug therapy. The need for this role extension stemmed from alarming reports showing high rates of preventable adverse drug events leading to hospital admissions and extra health care costs.

In the community pharmacy setting the first examples of patient-centered services related to medication counseling services. They started to evolve in the 1960's and 1970's as a consequence of drug catastrophes, particularly thalidomide, which set a demand for more open access to drug information to medicine users. The importance of more patient-centered clinical practice was recognized in a large scale in 1990, when Hepler and Strand published their landmark article "Opportunities and Responsibilities in Pharmaceutical Care" (Hepler and Strand 1990).

According to Hepler's and Strand's (1990) original definition: "Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life". Cure of disease, elimination or reduction of symptomatology, arresting or slowing of a disease process, and preventing a disease or symptomatology were stated as desired outcomes. Consistent with this definition, pharmaceutical care is provided for the direct benefit of the patient, and the pharmacist needs to collaborate closely with the patient, but also with other health professionals so that specific therapeutic objectives will be achieved (Hepler and Strand 1990).

Even if the current definition of pharmaceutical care has slightly changed from the original version, the principles and purpose remain the same (Cipolle et al. 1998, 2004). Pharmaceutical care is "a patient centered practice in which the practitioner assumes responsibility for a patient's drug-related needs and is held accountable for this commitment." The drug-related needs of a patient include 1) appropriateness of the medication; 2) effectiveness of the medication; 3) safety of the medication; and 4) compliance of the patient (Cipolle et al. 2004). If all of these drug-related needs are not met, a drug-therapy problem (DTP) exists. In pharmaceutical care, the responsibility of the practitioner is to ascertain, that all drug-related needs of the patient are met and to identify, resolve and prevent DTPs (Cipolle et al. 2004).

2.1.1 Patient Care Process in Pharmaceutical Care

In pharmaceutical care, a key idea is to provide standardised care for all patients during all encounters (Strand et el. 2004). As a result, standards of care have been developed for the

pharmaceutical care process (Table 1). The process includes 3 main activities: 1) assessment; 2) care plan development; and 3) follow-up evaluation (Cipolle et al. 2004, Strand et al. 2004).

Table 1. *The activities and standards of care for the process of pharmaceutical care (modified from Cipolle et al. 2004, Strand et al. 2004)*

ACTIVITY	STANDARDS OF CARE
ASSESSMENT	**1. Collection of patient specific information** The practitioner collects patient-specific information for decision-making concerning all drug therapies. This includes meeting with and collecting information from the patient. **2. Assessment of drug-related needs** The practitioner analyses the collected assessment data to determine if the patient's drug-related needs are being met. That is, all the patient's medications are appropriately indicated, the most effective available, the safest possible, and the patient is able and willing to take the medications as intended. **3. Identification of drug therapy problems** The practitioner analyses the assessment data to determine if any DTPs are present (includes prioritization of the DTPs to select the ones that need to be resolved first).
CARE PLAN DEVELOPMENT	**4. Development of goals of therapy** The practitioner identifies individualized goals of therapy for the patient. **5. Statement of interventions** The practitioner develops a care plan that includes interventions to resolve DTPs, achieve goals of therapy, and prevent DTPs. **6. Establishing a schedule for follow-up evaluations** The practitioner develops a schedule to follow-up and evaluate the effectiveness of drug therapies and assess any adverse events experienced by the patient.
FOLLOW-UP EVALUATION	**7. Follow-up evaluation** The practitioner evaluates the patient's actual outcomes and determines the patient's progress toward the achievement of the goals of therapy, determines if any safety or compliance issues are present, and assesses whether any new DTPs have developed.

Assessment. Before making any decisions, patient-specific data, e.g., demographic data, clinical information, medical history, medications, but also patient's attitudes, concerns, and medication taking behaviors need to be collected. As a part of the data collection, discussion with the patient is necessary for attaining all relevant information. The collected information is used to determine if the patient's drug-related needs are being met (Standard 2 in Table 1). Pharmacotherapy workup is a decision-making framework or process, by which these determinations can be done systematically (Figure 1).

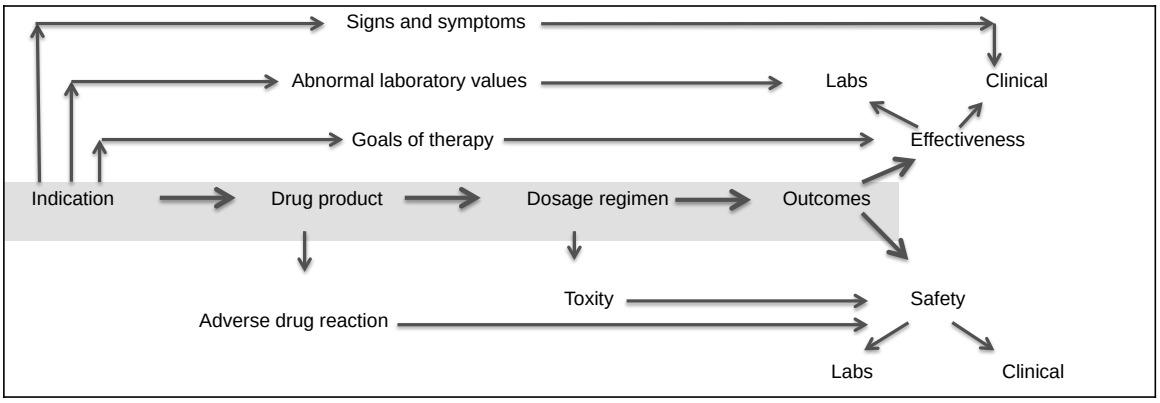

Figure 1 *Structure of the Pharmacotherapy workup for systematic assessment of patient's drug-related needs (Cipolle et al. 2004)*

The first step is to ascertain whether there is an indication for each medication, what product is used to treat the indication, what dosage is taken, and what has been the response (gray line in Figure 1). Also untreated indications need to be assessed. If there is an appropriate indication for all the used drugs, the outcomes of drug therapy are determined both in regard to effectiveness and safety (Figure 1). Effectiveness needs to be evaluated against the determined, desired goals of therapy based on laboratory values and by the signs and symptoms experienced by the patient (upper part of Figure 1).

In the next step the safety of drug therapy is assessed similarly to effectiveness (lower part of Figure 1). Unsafe pharmacotherapy can be related to the drug product, which is causing an ADR, or to too high drug dose causing toxity. After ascertaining the indication, effectiveness and safety of the drug therapy, the patient's compliance needs to be evaluated.

The order of assessing drug-related needs and making decisions is crucial, as there is no reason to judge medicine's effectiveness or safety, if there is no indication for it. Also, if the medication is not effective or safe, there is no need for the patient to be compliant. If all the patient's medications are not indicated, effective, safe or taken as indicated, a DTP is present. DTPs can exist at any phase of the decision-making framework (Figure 2). After DTPs are identified, they need to be prioritized and documented.

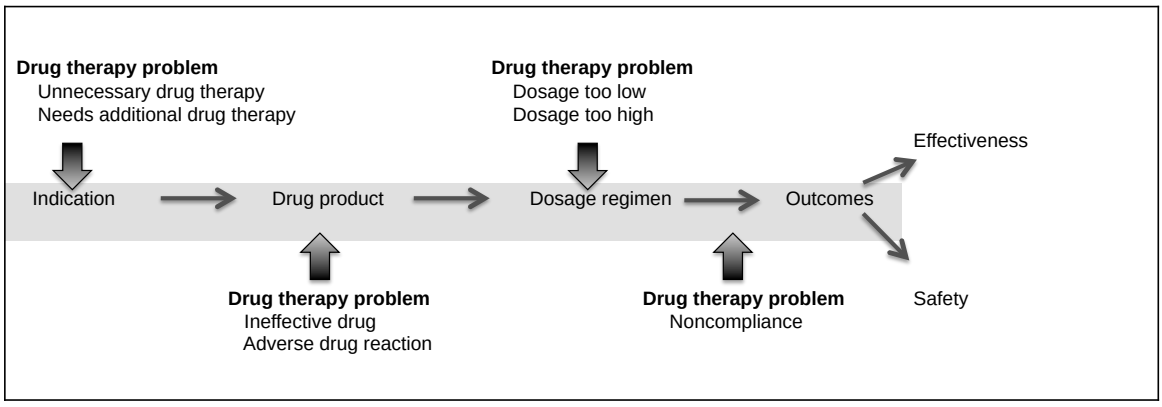

Figure 2 *Structure of the Pharmacotherapy workup and points where DTPs can occur (Cipolle et al. 2004)*

Care plan development. After assessment, individualized, realistic and measurable goals of therapy for each indication are identified (Cipolle et al. 2004). Then a care plan with interventions to resolve DTPs, achieve goals of therapy, and to prevent new DTPs is developed and documented. Both the therapeutic goals and the care plan are discussed with the patient, and when appropriate, also with other health care providers. In addition, a schedule for future follow-up and evaluation is documented.

Follow-up evaluation. Follow-up is important part of patient care process that aims to determine if the desired goals of therapy have been achieved. The outcomes need to be evaluated both for effectiveness and safety. During the follow-up it also needs to be assessed whether new DTPs have emerged.

2.1.2 Implementing Pharmaceutical Care Through Professional Services

Various pharmaceutical services and practices to implement the philosophy of pharmaceutical care have been developed in different countries (Berenguer et al. 2004, Farris et al. 2005, Figure 3). Cooperation with medicine users and communication on their medications is an essential part of any service designed to be an implementation of the philosophy, although patient counseling as such does not meet all the requirements of the definition of pharmaceutical care (McGivney et al. 2007).

Different disease management programs are typical services developed (Figure 3). They are available for example in the US, Australia and Portugal to improve clinical outcomes in some common chronic conditions, such as diabetes, asthma or hypertension (Farris et al. 2005, Knapp et al. 2005). These programs have been demonstrated to be successful in improving therapeutic outcomes and quality of life, and in decreasing health care costs (Cranor and Christensen 2003, Cranor et al. 2003, Bunting and Cranor 2006). These various disease management programs target to specific diseases and do not take into account the patient's entire drug regimen (McGivney et al. 2007). Thus, they do not necessarily address all "patient's drug-related needs" as stated in the definition of pharmaceutical care (Cipolle et al. 2004).

More comprehensive procedures that take into account all of the patient's clinical conditions and related medication needs have evolved in different countries under the concept of medication review (Sorensen et al. 2004, APhA and NACDS 2005, 2008, Pharmaceutical Society of Australia 2011). Medication review procedures apply patient counseling and disease management as elements to the patient-oriented service (Figure 3). These advanced procedures require close collaboration with other health care professionals, particularly with physicians (Chen and de Almeida Neto 2007, International Pharmaceutical Federation 2009).

Even if patient counseling as such is not considered as an implementation of pharmaceutical care, patient counseling services may serve as a first necessary step for community pharmacists towards taking more responsibility in patient care. This happened e.g., in Finland: the evolution of pharmaceutical care services started from national, coordinated efforts to improve patient counseling services in community pharmacies. For that purpose, a national program (TIPPA) was run in 2000–2003 (TIPPA Project 2004, Puumalainen 2005, Kansanaho 2006). The program aimed at patient-oriented communication practices (TIPPA=Customized Information for the Benefit of the Patient from the Community Pharmacy). All the key pharmacy stakeholders, including authorities, universities, continuing education centres and professional organizations were involved in this extensive program. As pharmacists started to communicate more with medicine users they started to see more of the many problems people have with their medications. It became evident that all of the problems cannot be solved by counseling, and community pharmacists could not solve them alone, without cooperating with other health care providers involved in the patient's care. As a result, a follow-up program for TIPPA was implemented in 2004–2007 which focused on developing more advanced community pharmacy services and strengthening collaboration between pharmacists and other local health care providers. The most important development under the follow-up program was establishment of the national procedure for collaborative comprehensive medication review (CMR) and related accreditation training (substudies II and III).

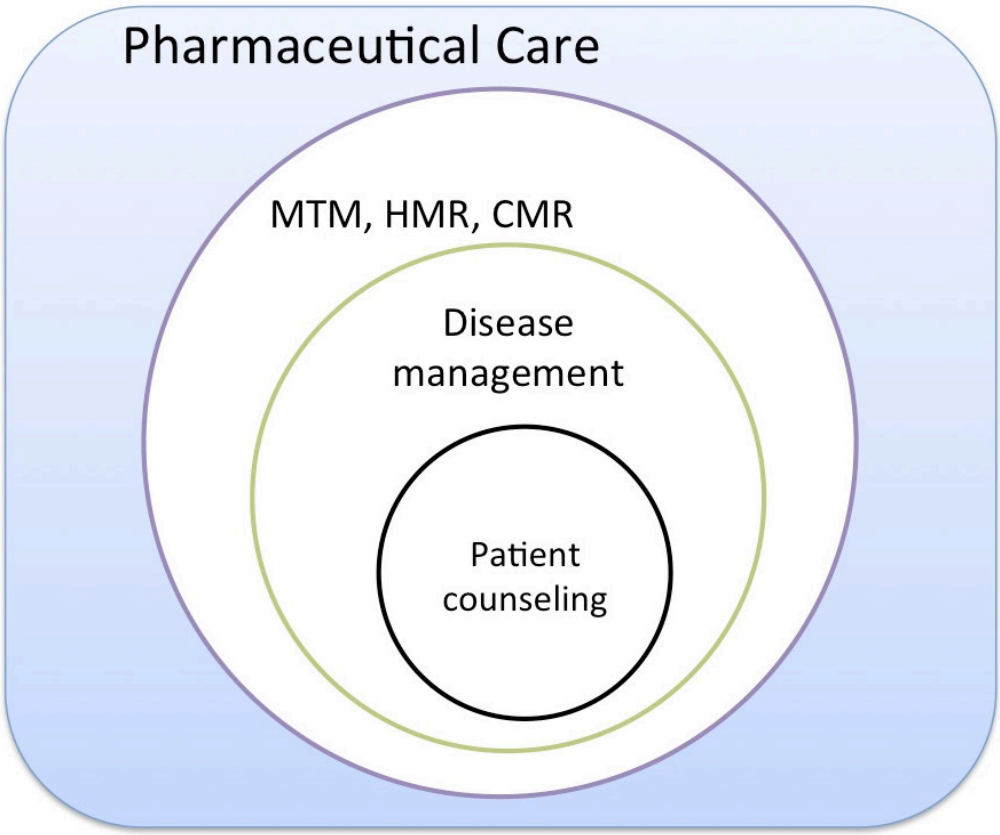

Figure 3 *Comprehensiveness of patient-oriented services based on the philosophy of pharmaceutical care (modified from McGivney et al. 2007). MTM=Medication Therapy Management (APhA and NACDS 2008), HMR=Home Medicines Review (Sorensen et al. 2004), CMR=Comprehensive Medication Review*

2.2 Medication Review

There are several definitions of the term medication review. The Australian National Prescribing Service (2000) has defined medication review as "a retrospective critical review of all prescribed, over-the-counter, and complementary (herbal) medications" with the aim to "optimise therapy and minimise medication-related problems". In the UK the task force on Medicines Partnership and the National Collaborative Medicines Management Services Programme places more emphasis on the patient in its definition "a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste" (Shaw et al. 2002). Pharmaceutical Care Network Europe has defined medication review as "an evaluation of patient's medicines with the aim of managing the risk and optimizing the outcome of medicine therapy by detecting, solving and preventing drug-related problems" (www.pcne.org).

Since the definitions of medication review are different, the actual medication review procedures created in different countries also differ (Lyles et al. 2001, Harjivan and Lyles 2002, Fulda et al. 2004, Sorensen et al. 2004, APhA and NACDS 2008, Australian Government 2011a,b). The procedures vary from reviews consisting mostly of patient counseling aimed at improving adherence, such as Medicines Use Review (MUR) in the UK (Department of Health 2005) to comprehensive clinical medication reviews, such as HMR in Australia (Sorensen et al. 2004, Pharmaceutical Society of Australia 2011) and MTM in the US (APhA and NACDS 2008). Some procedures assess the appropriateness of pharmacotherapy against predetermined criteria and standards at the patient level during dispensing, such as prospective Drug Utilization Review (pDUR; Fulda et al. 2004), or on the system level as Drug Regimen Review or retrospective DUR (rDUR; Lyles et al. 2001, Harjivan and Lyles 2002) in the US.

The Pharmaceutical Society of Australia defines medication review as "a systematic assessment of a consumer's medications and the management of those medications, with the aim of optimising consumer health outcomes and identifying potential medication-related issues within the framework of the quality use of medicines. The term 'medication review' encompasses a continuum of processes in various formats and complexities, ranging from an opportunistic discussion to a more comprehensive and proactive approach to reviewing the consumer's medication regimen" (Pharmaceutical Society of Australia 2010). This definition takes well into account the different levels of medication review.

Diversity of the medication review procedures has resulted in attempts to categorize various procedures by their characteristics and complexity (Shaw et al. 2002, Clyne et al. 2008, Pharmaceutical Society of Australia 2010). Shaw et al. (2002) classified medication reviews into four levels based on the patient involvement and the amount of clinical information available to the pharmacist (Table 2). Level 0 medication reviews are opportunistic, unstructured ad-hoc reviews. Level 1 prescription reviews are technical reviews of patient medication lists without access to medical records or discussions with the patient. Level 2 reviews, i.e., treatment reviews are also usually conducted without patient involvement, but they include access to full patient notes. Most comprehensive third level reviews, "clinical medication reviews", involve access to medical records, assessment of all medications, including OTC and complementary medicines, as well as a strong component of patient involvement.

Table 2. *Levels of medication reviews according to Shaw et al. (2002)*

Level 0	**Level 1**	**Level 2**	**Level 3**
Ad hoc review: An unstructured, opportunistic review	Prescription review: A technical review of list of patient's medicines (paper-based)	Treatment review: A review of medicines with patient's full notes (not necessarily with the patient present)	Clinical medication review: A face-to-face review of medicines and condition with the patient

The classification by Shaw et al. (2002) fails however to allow categorization of all medication review services available in different countries. For example, the MUR by community pharmacists in the UK is "a structured adherence-centred review" (Pharmaceutical Services Negotiating Committee 2011) which is conducted in collaboration with the patient, like the highest Level 3 medication review in the Shaw et al. (2002) classification. Still, during MUR, the pharmacist does not have access to full patient notes as should be the case even in Level 2 reviews.

Australian classification of medication reviews resembles the Shaw et al. (2002) classification, but is less precise (Figure 4). Different medication review procedures can be classified according to how complex and systematic they are. More complex procedures require additional training and skills from a pharmacist (Pharmaceutical Society of Australia 2010). However, the Australian classification is incomplete in describing patient involvement or clinical information available for the reviewing pharmacist.

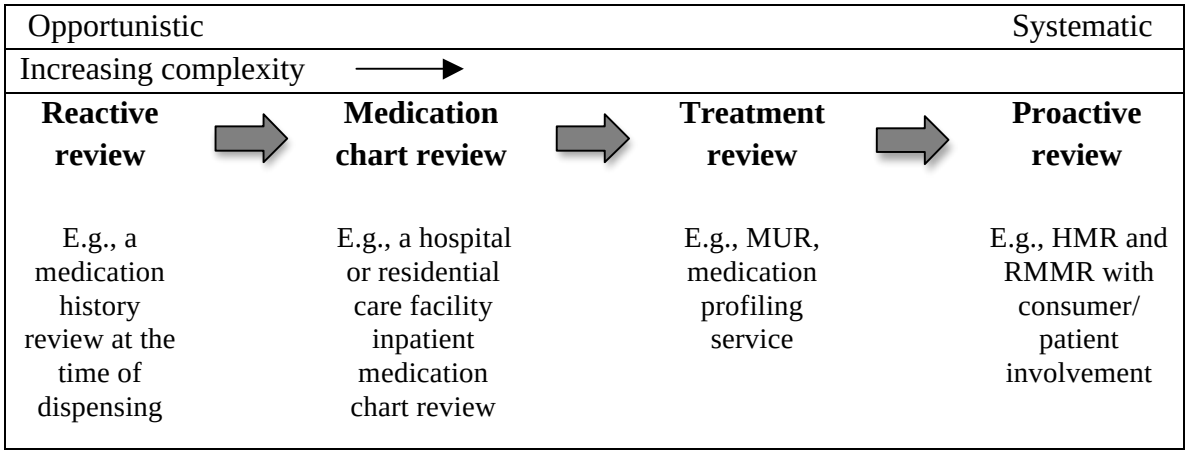

Figure 4 *Categorization of medication reviews according to the Pharmaceutical Society of Australia (2010, modified). MUR=Medication Use Review; HMR=Home Medicines Review; RMMR=Residential Medication Management Review.*

In conclusion, it is most appropriate to use a non-hierarchical classification of medication review procedures based on the purpose of the review as suggested by Clyne at al. (Table 3; Clyne et al. 2008). Type 1 reviews aim to address prescription-related technical issues, e.g., cost-effectiveness, without a requirement of a patient's presence. A prescription review may involve all prescriptions but may cover only one therapeutic area (Clyne et al. 2008). Type 2 "Concordance and compliance reviews" aim to explore patient's actual medicine use behaviours and factors that may influence medicines taking. Unlike type 1 reviews, OTC and complementary medications are included in type 2 reviews and patient involvement is usually needed. Type 3, clinical medication reviews are conducted with the patient present and with full access to patient's medical notes and laboratory test results which allows review of medications against clinical conditions. Thus, they are the most comprehensive procedures.

Table 3. *Types of medication review according to Clyne et al. (2008, modified)*

	Type 1 Prescription review	**Type 2 Concordance and compliance review**	**Type 3 Clinical medication review**
Purpose	Address technical issues relating to the prescription, e.g., anomalies, cost effectiveness	Address issues relating to the patient's medicine taking behavior	Address issues relating to the patient's use of medicines in the context of their clinical condition
Patient involvement	No	Patient usually present	Patient always involved
Access to patient notes, medications included	May include access to clinical patient notes, usually only part of prescription medications included	May include access to clinical patient notes, includes all prescription, complementary and OTC medicines	Includes access to clinical patient notes, includes all prescription, complementary and OTC medicines
Review of	Medicines	Medicines use	Medicines and condition

In addition to differing in complexity, patient involvement and availability of clinical patient information, various medication reviews also have dissimilarities with regard to level of multiprofessional collaboration and the setting where the reviews are conducted. Some review procedures are developed only for inpatient settings like Residential Medication Management Review (RMMR) in Australia. Other are aimed only at community-dwellers, like the HMR in Australia. In some procedures the pharmacist's communication with the physician is mandatory (HMR), in others the physician is contacted as needed (MUR).

The literature review for this thesis focuses on Type 3 (Clyne et al. 2008) clinical medication review procedures in outpatient settings focusing on studies describing reviews among elderly patients. Because HMR in Australia and MTM in the US were used as models when the Finnish CMR procedure was developed, only these two are described in more detail in the following chapters.

2.2.1 Medication Therapy Management (MTM)

Background

In the United States Johnson and Bootman estimated in 1995 that annual costs associated to mortality and morbidity due to DRPs in the ambulatory setting would amount to USD 76.6 billion (Johnson and Bootman 1995). When Ernst and Grizzle (2001) updated the estimate for year 2000, the annual costs of drug-related morbidity and mortality exceeded USD 177.4 billion. In 1998 it was estimated, that ADRs were between the fourth and sixth frequent cause for death in US hospitals (Lazarou et al. 1998). Among older outpatients the medication-related problems have been frequent in the USA with 50.1 ADEs occurring per 1000 person years (Gurwitz et al. 2003). It is noteworthy, that 27.6% of the ADEs were estimated as preventable.

The health care system in the USA is diverse because of the variety of insurance providers. The public sector is responsible for providing two types of insurance: state-managed Medicaid for low-income citizens, and government-provided Medicare for people aged >65 years, and for younger disabled persons (Christensen and Farris 2006). Most citizens however obtain insurance through their employers or purchase it themselves. The private sector is not required to follow the regulations of the public sector. Also the fact that the pharmacies in the US are regulated by the individual states instead of the Federal Government makes pharmacy services in different parts of the country diverse.

Various pharmaceutical care services for outpatients have been available in the US for almost two decades (Cranor et al. 2003, Kuo et al. 2004, Knapp et al. 2005, Stubbings et al. 2011). In some states' Medicaid programs pharmacists have been paid for resolving DRPs and providing disease management services for individual patients since the mid-1990's (Kuo et al. 2004). Also private payers have had successful programs to involve pharmacists in patient care almost as long (Cranor and Christensen 2003, Kuo et al. 2004). Different disease management programs have been successful in improving care results and quality of life, and in decreasing health care costs (Cranor and Christensen 2003, Cranor et al. 2003, Bunting and Cranor 2006, Bunting et al. 2008, Carter et al. 2009).

Nationally pharmaceutical care services became recognized in the US in 2003 when the Federal Government passed the Medicare Prescription Drug, Improvement and Modernization Act; MMA 2003 (The Medicare Prescription Drug, Improvement and Modernization Act 2003). MMA 2003 required that from January 2006 Medicare part D insurers provide Medication Therapy Management (MTM) services for their selected beneficiaries to optimize therapeutic outcomes by improving medication use and reducing adverse drug events (The Medicare Prescription Drug, Improvement and Modernization Act 2003, Pellegrino et al. 2009). MMA 2003 identified three key goals for MTM services: 1) provision of education and counseling to improve enrollee's understanding of their medication; 2) improvement of medication adherence; and 3) detection of ADRs and patterns of improper prescription drug use (MMA 2003, Pellegrino et al. 2009). Pharmacists were the only health care professionals specifically named as providers of MTM services. However, the MMA lacks detailed service requirements and patient

eligibility criteria, and determination of the details of service provision, including interventions were left to be determined by the Part D Providers (Medicare Prescription Drug, Improvement, and Modernization Act of 2003). In 2010, the minimum Medicare MTM eligibility criteria included drug cost threshold of USD 3000 for part D drugs, use of 2–8 drugs, and having 2 or 3 chronic conditions (Centers for Medicare & Medicaid Services 2010). In contrast to Medicare programs, MTM programs provided in the private sector rarely have specific eligibility criteria depending on specific number of drugs or condition or specific drug cost threshold (Abt Associates 2008).

As a response to MMA legislation, 11 US pharmacy organizations developed a consensus definition for MTM in 2004 (Bluml 2005). According to this statement MTM is "a distinct service or group of services that optimize therapeutic outcomes for individual patients" and are independent of provision of a medication product, but can occur in conjunction with that. Based on the consensus definition, MTM encompasses a wide range of activities and responsibilities based on the needs of the individual patient. These include, e.g., formulation of a medication treatment plan, monitoring and evaluating the patient's response to therapy, including safety and effectiveness, performing a comprehensive medication review to identify, resolve, and prevent medication-related problems, and providing information, support services, and resources designed to enhance patient adherence.

Operationally, MTM programs should provide individualized, patient-specific care. Face-to-face interaction between the patient and the pharmacist was defined as the ideal method for providing this care (Bluml 2005). In practice, MTM services vary from medication therapy reviews to anticoagulation management and immunization (Figure 5).

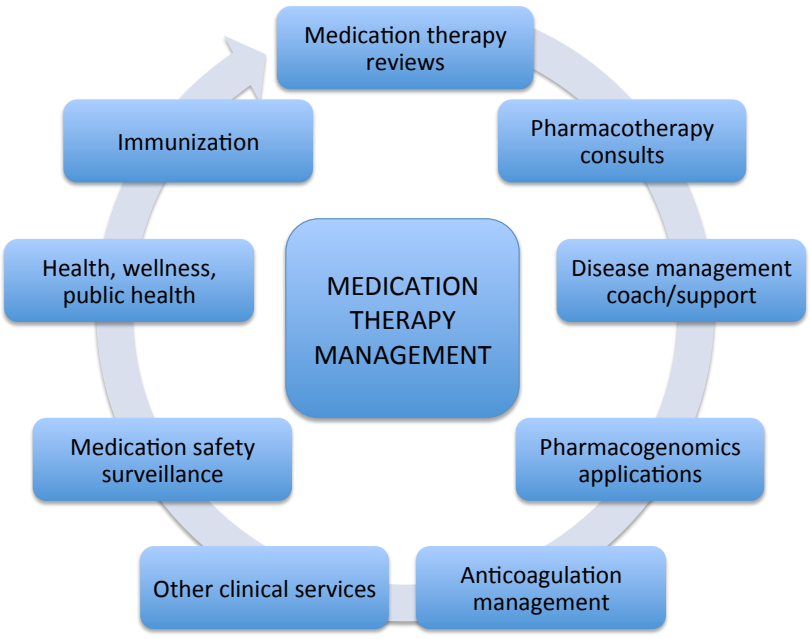

Figure 5 *Medication Therapy Management (MTM) services to optimize therapeutic outcomes (American Pharmacists Association 2011).*

Core Elements of MTM Service Model

Building on the MTM consensus definition (Bluml 2005), The American Pharmacists Association (APhA) and the National Association of Chain Drug Stores Foundation (NACDS) established a model framework for implementing MTM services in the community pharmacy setting (APhA and NACDS 2005). A 2008 update of the document focuses on providing MTM in settings where the patients or care givers can be actively involved in the process (APhA and NACDS 2008). In all, collaboration between patients, pharmacists, physicians and other health care professionals is important in the MTM service model.

According to the framework, MTM services include five core elements: 1) a medication therapy review (MTR); 2) an intervention and/or a referral; 3) a personal medication record; 4) a medication-related action plan; and 5) documentation and follow-up (Figure 6). The sequence of the elements can be modified according to the individual case.

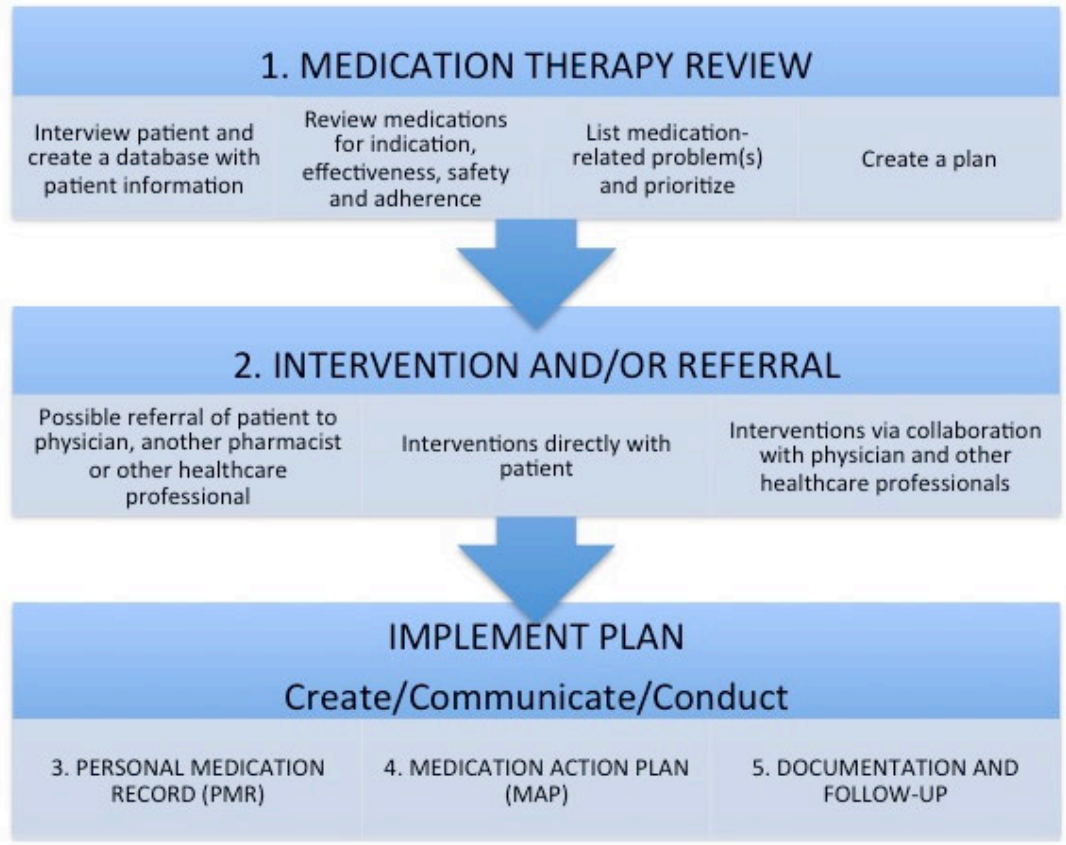

Figure 6 *Flowchart of the five core elements of MTM procedure (modified from APhA and NACDS 2008).*

Medication therapy review can be comprehensive or targeted, depending on the needs of the patient (APhA and NACDS 2008). In comprehensive MTR the patient provides the pharmacist with information of all medications taken, including OTC medicines and complementary medicines. The pharmacist may also gather data on e.g., medical history and patient thoughts and experiences of their pharmacotherapy. Interpretation of laboratory test results and assessment of quality of life can also be part of the procedure. The pharmacist reviews the medications for medication-related problems against the patient's complete medical and medication history. Consistent with the principles of pharmaceutical care (Chapter 2.1), DRPs related to indication, effectiveness, safety and adherence are covered (Figure 6). After identifying the problems, the pharmacist develops a care plan to resolve them. The interventions resulting from MTR depend on the nature of the problems (Figure 6), and may involve collaboration with physician or other health care professionals to agree on actions. Targeted MTRs are ideally meant to complement comprehensive MTRs, so that the pharmacist can monitor the patient's situation and address new medication-related problems.

In order to improve medication self-management, a personal medication record and a medication action plan are developed for the patient (APhA and NACDS 2008; Figure 6). The medication record includes a comprehensive list of the patient's medications, possibly complemented with indications, instructions for use and other useful information (APhA and NACDS 2008). The medication action plan contains actions for the patient's self-management of his/her conditions to achieve specific health goals. In 2010 Medicare required some kind of written or printed material of MTM to be provided to the patient, but medication action plan and personal medication record are stated only as possible options not as mandatory documents (Centers for Medicare & Medicaid Services 2010).

Follow-up MTM visits or transition of care are agreed on based on individual needs of the patient (APhA and NACDS 2008, Figure 6). All services and interventions are documented in order to follow patient progress and to be used in billing of the services.

The MTM procedure described in this chapter represents a preferred method of service delivery by pharmacists, but MTM guidelines have been developed also from the perspective of other stakeholders (Consensus Document Workgroup 2006, APhA and NACDS 2008, Pellegrino et al. 2009). For example, insurers prefer other than face-to-face methods of MTM delivery in their guidelines, in particular telephonic communication (Pellegrino et al. 2009).

Outcomes of MTM Studies

As a result of the lack of rigorous official guidance, the MTM services developed under Medicare part D have great variability in their patient eligibility criteria, type of services provided and the way services are provided (Touchette et al. 2006, Schommer et al. 2008 a,b, Centers for Medicare & Medicaid Services 2010). In addition, there are various MTM programs independent of Medicare. Many pharmaceutical care services implemented before the MTM legislation comply with the principles of MTM (Barnett et al. 2009, Ramalho de Oliveira et al. 2010). Since the early 2000's, these services have evolved

significantly changing from providing mainly patient education regarding acute medications towards services involving collaboration with prescribers and focusing more on cost-effective management of chronic conditions (Barnett et al. 2009). Simultaneously, the estimated cost avoidance due to diminished use of other health care resources increased from USD 24/encounter in 2000 to USD 429 in 2006 (Barnett et al. 2009).

Because of the significant variation in and evolution of MTM services, this literature review will focus on recent studies where the intervention is comparable to the core elements of MTM service model presented in the previous chapter (APhA and NACDS 2008) or complies with the standards of practice of pharmaceutical care (Cipolle et al. 2004, Strand et al. 2004; Table 1). Thus, the studies reviewed should have a pharmacist intervention that includes a direct patient contact and a MTR where the entire drug regimen is reviewed for effectiveness, safety, indication and adherence. According to the overall context of this thesis, i.e., elderly outpatients, studies that involve inpatients or only patients aged <65 years, e.g., employees, are excluded. However, MTM studies involving only elderly patients are rare, and thus, other studies with at least some elderly patients involved are included to provide better insight on the potential outcomes of MTM. Disease state management programs that focus solely on management of certain chronic conditions such as asthma or diabetes, and lack comprehensive review of the patient's complete medication regimen, were excluded. Overall, there are hundreds of studies examining patient-related outcomes of pharmacist-provided direct patient care in the USA. A meta-analysis of these studies indicates that pharmacist-provided care is beneficial in e.g., improving therapeutic outcomes, reducing ADEs and increasing adherence (Chisholm-Burns et al. 2010).

In total 17 published MTM studies matching the inclusion criteria were found (Table 4). The quality of most studies was good in relation to having a controlled study design and long follow-up periods (Table 4). However, several of the studies had a relatively small study sample or were based solely on retrospective analysis of MTM documentation and even if controlled, lacked randomization of patients (Table 4). Also, in several studies a significant proportion of patients were younger than 65 years.

Several studies indicate that MTM services can improve clinical health outcomes and result in cost-savings through avoidance of the need to use other health care resources (Isetts et al. 2003, 2008, Lewis et al. 2008, Fox et al. 2009, Planas et al. 2009, Ramalho de Oliveira et al. 2010; Table 4). Even if not the strongest in its methodology, the largest of such studies with the longest follow-up period was conducted in Minnesota, where a large health care provider organization, Fairview Health Services, implemented standardized pharmaceutical care service in 1998 (Ramalho de Oliveira et al. 2010). In the Fairview MTM program pharmaceutical care, including desired goals of therapy, change in clinical status at the follow-up encounters and estimated health care savings, are systematically documented by the pharmacists. According to a large retrospective study analyzing such MTM documentation of 9 068 patients during 1998–2008, more than half (55%) of the 12 851 medical conditions not at goal at enrollment improved during MTM and 23% were unchanged (Ramalho de Oliveira et al. 2010). For a subset of 110 patients with diabetes the therapeutic goals were met by 43% after MTM, compared to 17% at the initial visit. The pharmacist-estimated cost-avoidance per encounter, mostly due to avoided clinical

outpatient visits or hospitalizations, was USD 86, which exceeds the costs of MTM by USD 19/encounter. Another study using 4 years of pharmacists' MTM documentation from 2000 to 2003 (n=2 985) indicated that 32% of the total of 16 132 conditions improved as a result of MTM while there was no change in 56% (Strand et al. 2004). In this study the estimated cost avoidance was USD 98 per encounter, which is USD 50 more than the average cost of one MTM visit. Other studies from Minnesota indicate that MTM increases the overall percentage of therapeutic goals achieved from 74–76% to 89–90% according to pharmacists' documentation (Isetts et al. 2003, 2008, Table 4). According to chart audits, the proportion of patients meeting goals for hypertension (71% vs. 59%, p=0.03) and cholesterol (52% vs. 30%, p=0.001) was higher among MTM patients than among control patients with hypertension and hyperlipidemia (Isetts et al. 2008).

The IMPROVE study, a prospective RCT among high-risk patients of 9 Veterans Affairs Medical centers (n=523) evaluated the effect of MTM on several outcomes over a 1-year follow-up period (Ellis et al. 2000a, Malone et al. 2000, Malone et al. 2001, Table 4). Among a subgroup of patients with hypercholesterolemia (n=208) the total cholesterol levels (-17.7 vs. 7.4 mg/dl) and LDL (-23.4 vs. -12.8 mg/dl) decreased significantly more for intervention than for control patients (Ellis et al. 2000a). However, there was no difference in the proportion of patients achieving goal lipid values. With regard to HRQoL the bodily pain domain and change in health status -rating declined significantly less compared to controls over time (Malone et al. 2001). However, the changes were not considered to be clinically meaningful. The intervention had no effect on hospitalizations, but increased the number of clinic visits compared to the controls (p=0.003), mainly because of pharmacist encounters (Malone et al. 2000). However, there was no difference in overall health care costs (Malone et al. 2000). Consistently, in another non-randomized controlled study among patients with heart or lung disease (n=231) MTM had no effect on hospitalizations or total health care charges compared to controls, but resulted in significantly greater increase in the number of clinic visits (1.2 vs. -0.9) and medications (1.0 vs. 0.2) (Fischer et al. 2002).

Studies on the effects of MTM on hospitalizations show inconsistent results (Malone et al. 2000, Fischer et al. 2002, Taylor et al. 2003, Welch et al. 2009). Some studies show no effect compared to controls (Malone et al. 2000, Fischer et al. 2002). In a RCT conducted in Alabama MTM patients had significantly greater decrease in annual number of hospitalizations and emergency department (ED) visits compared to controls (Taylor et al. 2003). In Colorado, on the other hand, patients opting in to a MTM program (n=459) were more likely to have a hospitalization (OR 1.4) than the control patients opting out (n=336), but there was no difference in ED visit rates (Welch et al. 2009). However, the intervention patients were less likely to die than the controls (OR 0.5).

The economic impact of MTM is variable (Table 4). Several studies indicate that there is no effect on total health care costs (Malone et al. 2000, Fischer et al. 2002, Chrischilles et al. 2004). Beneficial results have been found e.g., in Minnesota, where total annual health care expenditures per intervention patient (n=285) decreased from USD 11 965 to USD 8 197 ($p<0.001$) according to claims data (Isetts et al. 2008). Thus, the reduction in other health care costs exceeded the cost of providing MTM services by 12:1. In Connecticut among a small group of Medicaid patients (n=88), annual health care cost

savings according to claims data were USD 472/MTM patient compared to the previous year (Smith et al. 2011). The savings of medication claims costs were even higher, USD 1123/patient. However, lack of a control group may skew the results. Some studies have shown no significant change in prescription costs (Christensen et al. 2007, Fox et al. 2009) and even increased costs have been reported (Isetts et al. 2008, Welch et al. 2009).

MTM can have a beneficial effect on appropriateness of pharmacotherapy (Taylor et al. 2003, Chrischilles et al. 2004). In two studies MTM improved the Medication Appropriateness Index and in one decreased the use of potentially inappropriate medications by elderly patients (Taylor et al. 2003, Chrischilles et al. 2004).

Patient satisfaction in MTM has been high (Christensen et al. 2007, Ramalho de Oliveira et al. 2010). In Minnesota a survey was administered to all 1132 patients enrolled to MTM program in 2008 (Ramalho de Oliveira et al. 2008). Of the respondents (n=317) 94% indicated that their overall health and wellbeing had improved after MTM. MTM has also increased patient knowledge on their medications (Taylor et al. 2003, Lewis et al. 2008). Still, results of the impact of MTM on adherence remain controversial (Taylor et al. 2003, Planas et al. 2009).

Table 4. *Studies on Medication Therapy Management (MTM) among home-dwelling people. Presented in alphabetical order.*

Reference State	Study design/method	Study population	Outcome measures	Main results
Chrischilles et al. 2004 Iowa	Prospective cohort study with a control group 9-month follow-up (114 pharmacies)	Medicaid enrollees: ≥4 medications, including ≥1 for 12 specific diseases (n=524 interventions, n=1 687 controls), mean age 53 years (28% aged ≥65)	Medication Appropriateness Index (MAI) Use of PIMs (Beers 1997) Health care utilization (inpatient, outpatient, medical service and ED utilization and charges)	MAI score improved (from 9.4 to 8.3, p<0.001) Proportion of recipients aged 65 years or older using inappropriate medications decreased (from 43% to 32%, p<0.05) No difference in health care utilization or charges between cases and controls.
Christensen et al. 2007 North Carolina	Before-after study with claims analysis 6 months before and after MTM, 2 control groups	Polypharmacy patients enrolled to State Health Plan (n=67), mean age 68 years, 60% aged ≥65, 2 control groups (n=689, n=870)	DTPs* Number and costs of dispensed medications Patient satisfaction with services	Prescription drug use decreased only among control group patients. No change in prescription costs. Patients valued the service (89% were satisfied with the review of medications and quality of information provided by the pharmacist)
Ellis et al. 2000a Multicenter	Multicenter RCT 1-year follow-up	Patients from 9 Veterans Affairs medical centers meeting ≥3 of predetermined 6 criteria e.g., ≥5 medications, ≥3 diseases (n=208 interventions, n=229 controls), mean age 67	Change in cholesterol and LDL Achievement of goal lipid values Overall costs (hospitalizations, clinic visits, drug costs, laboratory costs)	Greater positive change in the total cholesterol and LDL in the intervention group (p<0.05) No differences between groups in patients achieving goal lipid values or in overall costs
Fischer et al. 2002 Minnesota	Non-randomized, controlled trial (pre-post with comparison group) 1-year follow-up	HMO enrollees with heart or lung disease in 3 intervention (n=231) and 3 control pharmacies (n=444), aged ≥18, mean age 57	Change in: Number of clinic visits, Number of unique medications Total (inpatient, outpatient, pharmacy) charges DTPs*	Greater increase in number of clinic visits (p<0.01) and number of unique medications (p<0.05) compared to controls No difference in total number of prescriptions dispensed, mean number of hospital days, proportion with hospital admission or total charges

Reference State	Study design/method	Study population	Outcome measures	Main results
Fox et al. 2009 Florida	Quasiexperimental, controlled study (2 control groups) 1-year follow-up	Medicare enrollees with diabetes, ≥3 chronic conditions, ≥4 drugs, estimated annual drug costs >USD 4000. (n=255 MTM, n=56 MTM eligible not having MTM, n=1 803 not MTM eligible, having comprehensive diabetes care), mean age 68 years	LDL Drug costs (9 first months of the intervention year vs. 9 first months of the following year)	Higher proportion of patients in the MTM group (69%) had appropriate LDL levels compared to MTM nonparticipants (50%) and enrollees with comprehensive diabetes care (54%), p<0.001 Average LDL in the MTM group was lower (83 mg/dl) compared to the diabetes care patients (94 mg/dl; p<0.001), but not to MTM non-participants (91 mg/dl) No significant drug cost savings compared to controls
Isetts et al. 2003 Minnesota	Retrospective review of MTM documentation Jan 1999–March 2002 Retrospective evaluation of pharmacists' clinical decisions by a 12-member expert panel	Patients seen at 6 Fairview clinics (n=2 524), 48% aged ≥65 years (range 3–97 years)	Rate of therapeutic goals achieved as documented by pharmacists (n=16 406 medical conditions) Quality of pharmacists' therapeutic determinations (sample of 15 patient records)	The rate of therapeutic goals achieved increased from 74% to 89% of the medical conditions 94% of the pharmacists' decisions were clinically credible
Isetts et al. 2006 Minnesota	Prospective study with matched controls (for patients' perception of care) Uncontrolled before-after study (for HRQoL) 6 months follow-up	Patients with expected high resource use and ≥1 of 12 conditions (n=285 interventions in 6 clinics, 285 matched controls in 9 clinics), median age 54 years (range 20–85), 14% aged ≥65 years	Patients' perception of care HRQoL (SF-12)	No difference in perception of care between interventions and control patients Improvement in 3 of 10 dimensions of HRQoL: physical role (p=0.001); social functioning (p=0.014); and physical component summary scale (p=0.024) in the intervention group

Reference State	Study design/method	Study population	Outcome measures	Main results
Isetts et al. 2008 Minnesota	Prospective study with control groups (for hypertension and hypercholesterolemia) Uncontrolled before-after study based on MTM documentation (for all goals of therapy) 1-year follow-up	Same study group as in Isetts et al. 2006 (n=285 interventions, n=126 comparisons with hypertension and n=128 with hyperlipidemia)	DRPs* Proportion of intervention patients' all goals of therapy achieved as documented by pharmacists Proportion of patients achieving goals for hypertension and hypercholesterolemia based on chart audit Total health expenditures (facility, medical and prescription claims) 1 year before and after MTM	Percentage of intervention patients' goals of therapy achieved increased from 76% to 90% Proportion of patients meeting goals for hypertension (71% vs. 59%, p=0.03) and cholesterol management (52% vs. 30%, p=0.001) was greater in the intervention than control group Total annual health expenditures/intervention person decreased 32% from USD 11 965 to USD 8 197 (p<0.001), even if drug costs increased by 12%
Lewis et al. 2008 Michigan	Uncontrolled prospective study 3 months follow-up	Patients with ≥4 long-term medications (n=67), aged ≥18, mean age 69 years, 60% aged ≥65 years	Pharmacists' recommendations* Patient knowledge on medications, diagnoses, and healthy lifestyle practices Patients' opinion on their health Effects on patient outcomes as assessed by pharmacists	Patient knowledge better at final evaluation compared to initial assessment (p<0.001) 59% of patients indicated improved health at follow-up visit Pharmacists evaluated that disease control improved for 75% of patients, adherence improved for 56% and adverse effects decreased or were avoided for 66%
Malone et al. 2000 Malone et al. 2001 (Same data as in Ellis et al. 2000a)	RCT 12 months follow-up	Patients from 9 Veterans Affairs medical centers meeting ≥3 of 6 predetermined criteria (e.g., taking ≥5 drugs, ≥3 chronic conditions) (n=523 interventions, n=531 controls), mean age 67 years	Health care resource utilization 12 months before and after the intervention (number of clinic visits, number of drug fills, hospitalizations, clinic and total health care costs) HRQoL (SF-36)	Number of clinic visits increased more for intervention patients (p=0.003) No difference in number of hospitalizations, prescription fills or total health care costs between groups Intervention patients declined less than controls for bodily pain domain (-2.4 vs. -6.3 units; p=0.004) and for change in health status -rating (-6.3 vs. -2.4 units; p<0.004), not considered as clinically significant. No difference in other HRQoL domains.

Reference State	Study design/method	Study population	Outcome measures	Main results
Planas et al. 2009 Oklahoma	RCT 9 months follow-up	Patients with diabetes and hypertension, (n=32 interventions, n=20 controls), mean age 64 years	Systolic blood pressure (SBP) % at goal blood pressure (BP) Antihypertensive medication Adherence	Mean SBP decreased 17.32 mmHg, increased 2.73 mmHg in controls (p=0.003) Proportion of patients at goal BP increased from 16% to 48%, decreased from 20% to 7% in controls. Intervention patients 12.9 times more likely to achieve goal SBP (p=0.021) No difference in the mean adherence rate.
Ramalho de Oliveira et al. 2010 Minnesota	Retrospective analysis of electronic MTM documentation 1998–2008 Patient satisfaction survey for new MTM enrollees in 2008	Patients enrolled in Fairview Health Service's MTM program, aged ≥21 (n=9 068), 45% aged ≥65 years	DRPs* Change in clinical outcome status as evaluated by the pharmacist during follow-up Estimated cost-avoidance Clinical status of diabetes (n=110) Patient satisfaction (n=317, response rate 28%)	Of the 12 851 medical conditions not in goal, 55% improved during MTM. Proportion of diabetics meeting clinical goals increased (17% vs. 43%) Pharmacist-estimated cost-saving of USD 2.9 million, USD 86/encounter Cost of providing MTM USD 67/encounter (return of investment 1.29) 94% of respondents agreed that their overall health and wellbeing had improved.
Smith et al. 2011 Connecticut	Uncontrolled before-after study with claims analysis 12 months before and after MTM	Medicaid patients, mean age 51 years (n=88)	DTPs* Annual health care costs (total medical, hospital, pharmacy and ED Medicaid claims)	Total annual cost saving compared to the year before MTM) USD 434 465/study group. Annual medication claim cost saving USD 1123/patient. Annual cost saving USD 472/patient for medical, hospital and ED visits.
Strand et al. 2004 Minnesota	Retrospective review of 4 years of electronic pharmaceutical care documentation	Patients aged 18–100 years, 52% aged >65 years (n=2 985)	Change in clinical status Health care cost savings (both evaluated by pharmacists)	Clinical status improved for 32% of the total 16 132 medical conditions, no change for 56%. Total health care savings USD 1 134 162, mostly relating to avoiding outpatient clinic visits (USD 585 650), return of investment 2:1

Reference State	Study design/method	Study population	Outcome measures	Main results
Taylor et al. 2003 Alabama	RCT 12 months follow-up	High risk patients of 3 family medicine clinics with 3 or more of 6 risk factors, e.g., ≥5 medications, ≥3 diseases (n=33 intervention, n=36 control), mean age 64 years	Annual hospital and ED visits compared to the year before enrollment Meeting of therapeutic goals in hypertension, diabetes, anticoagulation and dyslipidemia MAI index HRQoL (SF-36) Medication compliance scores Medication knowledge	Greater decrease in annual number of hospitalizations (-22 vs. 0; p=0.003) and ED visits (-12 vs. 0; p=0.044) compared to controls Proportion of patients responding to hypertension, diabetes, dyslipidemia and anticoagulation therapy increased significantly in the intervention group and decreased in the control group. MAI index improved in all 10 domains, decreased in 5 domain for controls. No difference in HRQoL between groups. Medication compliance scores improved in intervention, not in control group. Medication knowledge scores improved 36%, decreased 15% in control group (p<0.0001)
Welch et al. 2009 Colorado	Nonrandomized controlled study (opt-out patients as controls) Follow-up 180 days	Medicare enrollees with ≥2 chronic conditions, ≥5 medications, at least USD 4000 medication costs (n=459 opt-in, n=336 opt-out), mean age 69 years	Mortality Health care utilization (hospitalization, ED visits) Prescription medication costs (changes 180 days following the intervention) DRPs*	Opted-in less likely to die (OR 0.5), but more likely to have a hospitalization (OR 1.4) or increased medication costs (OR 1.4) No difference in ED visit rates between groups

DRP=Drug-related problem, DTP=Drug therapy problem, ED=Emergency department, HRQoL=Health-related quality of life, MAI= Medication Appropriateness Index (Hanlon et al. 1992), OR=Odds ratio, PIM=Potentially inappropriate medication, RCT=Randomized controlled study
* Results on drug-related problems are presented in Table 10.

2.2.2 Home Medicines Review (HMR)

Background

In Australia 2–4% of hospital admissions, i.e., approximately 150 000 admissions annually, are estimated to be medication-related (Runciman et al. 2003). Among elderly Australians as much as 26% of hospital admissions have been attributable to ADEs. Of medication-related hospital admissions, 32–77% are estimated to be preventable. In the community setting in Australia there are 10 million physician consultations every year, more than 10% of all general practitioner (GP) visits, estimated to involve a patient with an ADE, the problem being more common among older people (Miller et al. 2006).

In the late 1980's and early 1990's the Australian government recognized the need to improve the quality and safety of medication use in aged care facilities (Roughead et al. 2003). As a result, the first medication review service in Australia, the Residential Medication Management Review (RMMR), was granted commonwealth funding in 1995 by the Australian Government Department of Health and Ageing (Roughead et al. 2003). The RMMR services are aimed at permanent residents of aged care facilities, and thus, are not in the scope of this literature review. Nevertheless, studies of pharmacist-provided services in aged care facilities resulted in positive outcomes including medication cost savings, improvement of quality of life and decreased use of potentially harmful medicines, such as benzodiazepines (Roberts et al. 2001, Roughead et al. 2003). As a result, funding for medication review services for home-dwelling elderly was agreed on in 2000 (Commonwealth of Australia 2000) and introduced in the Medical Benefits Scheme in 2001 (Benrimoj and Roberts 2005).

HMR Procedure

The Home Medicines Review (HMR), earlier referred as Domiciliary Medication Management Review (DMMR), is aimed at home-dwelling people to maximize benefits of medicine regimen and prevent medication-related problems (Australian Government 2011b). The main objective is to achieve safe, effective and appropriate use of medications by detecting and addressing medication-related problems, to improve the patients' quality of life and health outcomes, and to increase the patients' and health professionals' knowledge on medicines.

Cooperation between health professionals is important in HMR. The procedure involves the patient's general practitioner, an accredited pharmacist, and other relevant health care practitioners, e.g., community nurses or carers, as well as the patient's regular community pharmacy (Pharmaceutical Society of Australia 2011). From the development phase of HMR, close collaboration between community pharmacists and GPs was seen as a key to successful establishment of new clinical pharmacy services in the ambulatory care setting (Chen et al. 1999a, Roberts et al. 2005) and innovative initiatives to enhance the collaboration were taken (Chen et al. 1999b).

The pharmacist providing HMR must be accredited by the Australian Association of Consultant Pharmacy or the Society of Hospital Pharmacists of Australia (Australian Association of Consultant Pharmacy 2011, Pharmaceutical Society of Australia 2011). The accreditation process includes completing a preparatory training course, submission of a mandatory portfolio of experience, and completing a multiple-choice-question exam and a case-study-based assessment. The accreditation must be renewed annually by a self-assessment survey and completion of a continuing professional development log for the previous 12 months. The multiple-choice-question exam is repeated every three years.

The HMR follows a systematic structure (Figure 7). Patients likely to benefit from HMR may be identified by a GP, hospital pharmacist at discharge, community pharmacist, another member of the health care team, the patient, or their care giver (Pharmaceutical Society of Australia 2011). The HMR process is officially initiated by the GP who determines that the review is clinically necessary to ensure quality use of medicines or to address patient's needs (Australian Government 2011b). Examples of risk factors that may result in referral for HMR include e.g., patients that are taking ≥5 regular medicines, more than 12 doses of medicines per day or a medicine that has narrow therapeutic index or requires therapeutic monitoring (Australian Government 2011b, Pharmaceutical Society of Australia 2011). In addition, patients with symptoms suggestive of an ADR, or who are seen by a number of different physicians, or who have been recently discharged from hospital or had remarkable changes in their medicines, or have difficulty managing their medicines because of e.g., impaired sight are also likely to benefit from HMR.

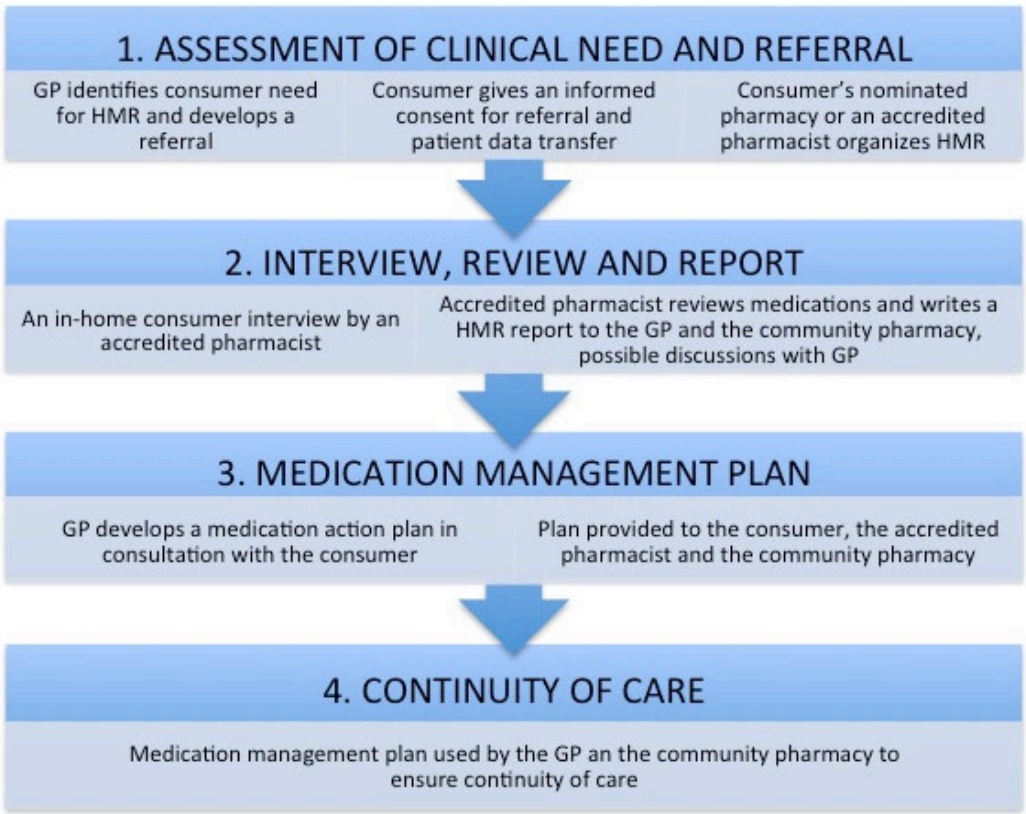

Figure 7 *HMR flowchart diagram (Pharmaceutical Society of Australia 2011, modified)*

The GP obtains an informed consent from the patient and makes a referral with relevant patient information to the patient's preferred pharmacy or directly to an accredited pharmacist (Pharmaceutical Society of Australia 2011). An accredited pharmacist conducts a patient interview, preferably at the patient's home. The aim of the interview is to collect information to inform the HMR report and to provide medicines- and health-related education and support. The responsiveness to home visits has been good, as it provides a comfortable environment for conversation compared to the pharmacy and gives an opportunity to ask questions and learn more about medications in familiar surroundings (Chen and Larkin 2002). The findings from the patient interview together with clinical patient data are used to conduct the review and to identify range of medication-related problems (Pharmaceutical Society of Australia 2011). These include:

- Medication use without indication
- Untreated indication
- Improper drug selection, including inappropriate cost-effectiveness
- Sub-therapeutic dosage, overdosage
- Continued use of medication for a condition that has been resolved or step down therapy for a condition that is well controlled
- ADRs
- Drug-drug, drug-disease, drug-food or drug-laboratory test interaction
- Failure to receive medication
- Dose/drug related issues, such as confusing schedules, storage issues, dosage forms, dosing interval, timing or dosing
- Medication management issues, such as incorrect medication use
- Incorrect use and suitability of, or the need for, compliance aids, therapeutic devices and appliances
- Need for written/verbal information and education regarding safe and effective use of medications, therapeutic devices, compliance aids and self care activities

In order to identify potentially inappropriate prescribing, the following tools are suggested to be used as reference guides (Pharmaceutical Society of Australia 2011): Drug Burden Index (Hilmer et al. 2007); The Beers criteria (Fick et al. 2003); McLeod criteria (McLeod et al. 1997); The Medication Appropriateness Index (MAI) (Hanlon et al. 1992); the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START) (Gallagher et al. 2008a); and/or the Australian Prescribing Indicators Tool (Basger et al. 2008). Several software programs are available for the pharmacists to assist in conducting the reviews and reporting the findings to physicians (Rigby 2004). Some of the programs also contain decision support tools (Rigby 2004).

After reviewing medications the pharmacist prepares a written report with findings and evidence-based recommendations. The report is sent to the referring GP and the patient's preferred pharmacy. The pharmacist may discuss the findings with the GP, but a face to-face case conference is not mandatory even if it has resulted in higher acceptance rate of pharmacist recommendations by physicians than a written report (Penrose-Wall et al. 2004). The GP discusses the recommendations with the patient and prepares a medication

management plan with agreed therapeutic goals, treatment regimens and lifestyle adjustments (Pharmaceutical Society of Australia 2011). The management plan is delivered to the community pharmacy to be used as a basis for ongoing follow-up, monitoring and support.

Outcomes of HMR Studies

The outcomes of HMR studies were assessed by searching articles from the databases PubMed and Scopus and by completing the search with articles retrieved from the reference lists of reviewed relevant articles and received from collaborative Australian researchers. Two comprehensive reports about HMR Program were used to ascertain that all relevant articles were found. The first was prepared by Urbis Keys Young for the Pharmacy Guild of Australia in 2005 to evaluate the pharmacy component of the HMR Program. It included HMR-related literature review up to April 2005 (Urbis Keys Young 2005). The second was prepared by Campbell Research & Consulting (2008) for the Australian Department of Health & Ageing, Medication Management & Research Section. Their report included review of medication management and HMR Program related articles, including grey literature from 2005 to January 2008. In addition, the report included articles retrieved by a public call for submissions. Based on the two reports, there is no strong clinical evidence to support the effectiveness of HMR (Urbis Keys Young 2005, Campbell Research and Consulting 2008).

A total of 9 HMR-related studies published in the scientific literature and three research reports were retrieved for this literature review (Nissen and Tett 2002, Urbis Keys Young 2005, Stafford et al. 2011, Table 5). Several of the studies have small study populations or are otherwise methodologically weak (Table 5). This is particularly true of the research report by Urbis Keys Young (2005). The study is based on an interview of patients (n=57) who had received a HMR 3–12 months earlier. During the interview, they retrospectively evaluated their HRQoL and health care use before and after HMR – a method which cannot be considered as reliable. In addition, 7 of the 12 retrieved studies were partly or entirely based on an analysis of HMR case reports (Table 5).

Only two randomized, controlled trials have been published regarding outcomes of HMR services (Sorensen et al. 2004, Nissen and Tett 2005, Table 5). In the first study pharmacists made to physicians an average of 6.8 recommendations per intervention patient (n=110), of which 54% were acted on (Sorensen et al. 2004). Six months after the intervention physicians reported that the proportion of intervention patients experiencing ADEs had decreased from 37% to 9% while there was no significant change for the control patients (Sorensen et al. 2004). There were no statistical differences in the number of hospital admissions, cumulative bed days, number of GP visits, self-reported ADEs, severity of illness scores or HRQoL between intervention and control patients. The intervention had no effect on medication costs and only an ongoing trend towards reduction in healthcare service costs. According to the authors, the lack of statistical significance might be due to the short duration of the study. Regardless of poor actual

study outcomes, 92% of GPs and 94% of pharmacists perceived that HMR had improved the care of participating patients (Sorensen et al. 2004).

The second RCT was a project funded by the Australian Government Department of Health and Ageing and involved patients from two rural study sites (Nissen and Tett 2005). Pharmacists made on the average 7.6 recommendations per intervention patient (n=88), of which 61% were accepted by physicians. Analysis of the recommendations revealed that 91% of them were evidence-based. When using both Pharmaceutical and Medical Benefit Scheme data, annual before-after health care costs rose for both intervention and control patients, but the increase was AUD 1411 lower for intervention patients. However, the intervention had no effect on the patients' HRQoL when measured after 12 months.

Only two studies of the economic effects of HMR (Krass and Smith 2000, Stafford et al. 2011) were retrieved in addition to the two RCTs described earlier. The first was based on an analysis of HMR case reports and a GP survey to see if the changes suggested by community pharmacists were implemented (Krass and Smith 2000). In the first phase of the study pharmacists conducted HMRs while attending a HMR training program and in the second phase the same pharmacists conducted additional HMRs after the training. In the phase I study, 2.5 changes in drug treatment had been implemented per patient three months after HMR. The corresponding figure was 3.4 changes per patient in phase II (Krass and Smith 2000). The changes resulted in a significant reduction in the mean number of medications per patient and in significant medication cost-savings which were greater than AUD 200 per year (Table 5). A clinical expert panel reviewed 141 HMRs conducted in phase II of the study. Of the patients (n=103) with drug regimen changes the panel rated at least 40% of the changes as leading to a significant positive effect on the patient's health.

In the study by Stafford et al. (2011) pharmacists' HMR reports and physicians' medication management plans prepared after HMR were used to count the effect of HMR on drug costs (n=560). Annual drug cost savings were only AUD 20 (Table 5), which is not surprising since the most common DRPs reported by pharmacists were untreated indications (Table 11). In the same study a subgroup of 180 cases were analyzed by experienced physicians and clinical pharmacists to estimate the probable clinical consequences that were avoided as a result of HMR. Each assumed consequence was linked to predetermined values for quality of life and health care resource utilization by the researchers. The interventions were not cost-effective, as the gain in quality of life was small and savings in health care costs (AUD 128) were AUD 200 less than the cost of HMR (Table 5). Because the assumptions on clinical outcomes resulting from HMRs were based solely on expert opinions, the reliability of the results is questionable.

The outcomes of HMR may differ depending on the patient population involved. In a retrospective cohort study among veterans treated for heart failure HMR delayed the time to hospitalization (Roughead et al. 2009). After adjustment for confounding factors HMR patients (n=273) had a 45% reduction in the rate of hospitalization at any time compared to controls (n=5 444, Roughead et al. 2009; Table 5). Also among veterans using warfarin, HMR (n=816) reduced the likelihood of hospitalization for bleeding by 79% compared to controls (n=16 320) between 2 and 6 months after the HMR (Roughead et al. 2011).

However, the effect was not sustained 6–12 months after the review, which may indicate that patients treated with warfarin and at high risk for bleeding might benefit from biannual HMRs.

Despite of lacking or modest evidence on beneficial clinical or humanistic patient outcomes, HMRs may result in improved and safer pharmacotherapy. First, pharmacists visit patients at home and may inform physicians of drug use they would not otherwise be aware of (Bell et al. 2006). For example in a HMR study the mean number of drugs used by mental health patients was significantly higher in the reports of pharmacists compared to those by physicians (7.8 vs. 9.1; $p<0.001$) (Bell et al. 2006). Second, as described in more detail in Chapter 3.2.2, pharmacists are able to recognize and report a high number of DRPs to physicians during HMR (Krass and Smith 2000, Roughead et al. 2004, Sorensen et al. 2004, Bell et al. 2006, Stafford et al. 2009, Castelino et al. 2011). Physicians have accepted 46–90% of pharmacists' recommendations (Bell et al. 2006, Castelino et al. 2011) and 35–54% of findings have resulted in change of drug regimen or been actually acted on (Krass and Smith 2000, Gilbert et al. 2002, Sorensen et al. 2004). The relatively low acceptance and implementation rates don't necessarily reflect the reliability of pharmacists' recommendations (Castelino et al. 2011). Among patients aged ≥65 years more than 90% of pharmacists' recommendations during HMR have been consistent with existing evidence-based guidelines for drug use in older adults (Castelino et al. 2011). Still, the physician acceptance rate in the same study was only 55%.

Two studies that analyzed pharmacists' recommendations from HMR case reports indicated that the recommendations could improve the appropriateness of pharmacotherapy and reduce the use of PIMs, if acted on (Castelino et al. 2010a,b, Table 5). In the first study (Castelino et al. 2010a) 40% (n=148) of older HMR patients (n=372) were using PIMs according to the Beers 2003 criteria (Fick et al. 2003). If the pharmacists' recommendations were implemented, 28% (n=105) of the patients would be using PIMs after HMR. This corresponds to a 29% reduction in the number of PIM users (Castelino et al. 2010a). Implementation of the pharmacists' recommendations during HMR could also significantly improve The Drug Burden Index, which is a tool that measures total exposure to drugs that possess anticholinergic and/or sedative properties (Hilmer et al. 2007, Castelino et al. 2010a). In a HMR study among elderly patients (n=270) mean Medication Appropriateness Index (MAI) score improved significantly based on the assumption that pharmacists' recommendations were accepted by physicians (Castelino et al. 2010b). Results on the actual uptake of pharmacists' recommendations (n=102) also revealed significantly lowered MAI scores after HMR (Castelino et al. 2010b).

In addition to HMR, other medication review services involving pharmacists in the Australian community setting have been studied (Stewart et al. 1998, Graffen et al. 2004). These interventions have lacked patient interview (Graffen et al. 2004) or focused mainly on patient education and counseling instead of clinical medication review (Stewart et al. 1998) and are thus beyond the scope of this literature review. Also, studies on post-hospital discharge HMRs are excluded, because the procedures do not always comply with the HMR procedure described in this chapter (Nguyen et al. 2007, Yu et al. 2007, Ponniah et al. 2008, Vuong et al. 2008, Lövgren et al. 2009, Angley et al. 2011).

Table 5. *Studies on Home Medicines Review (HMR) in Australia (includes 9 studies found in scientific literature and 2 project reports*). Presented in alphabetical order.*

Reference	Study design/method	Study population	Outcome measures	Key findings
Bell et al. 2006	Retrospective analysis of HMR referrals and case reports	Patients with mental illness (n=49) selected by 11 GPs, aged 21–87 years, mean age 66 years	Drug use Pharmacists' findings (i.e., DRPs) and recommendations[a]	Pharmacists identified higher incidence of drug use than documented by physicians (mean 9.1 drugs/person vs. 7.8; p<0.001)
Castelino et al. 2010a	Retrospective analysis of HMR case reports send to AACP for reaccreditation (n=148) and from 7 individual HMR service providers (n=224)	Community-dwelling people aged ≥65 years (n=372), mean age 76 years	Change in Drug Burden Index (DBI) score and PIM use if pharmacists' recommendations will be acted on	Significant reduction in the sum total of DBI scores for all patients (207 vs. 157; p<0.001) Decrease in % of patients exposed to DBI medications (61% vs. 52%) and PIMs (40% vs. 28%)
Castelino et al. 2010b	Retrospective analysis of HMR case reports from 7 pharmacists	Community-dwelling people aged ≥65 years (n=270), mean age 75 years	MAI scores at baseline, based on pharmacists' recommendations, and following GP uptake of recommendations (n=102)	Significant decrease in mean MAI score both based on recommendations (18 vs. 9) and following GP uptake of recommendations (19 vs. 12) (p<0.001)
Castelino et al. 2011	Retrospective analysis of HMR case reports from 7 pharmacists	Community-dwelling people aged ≥65 years (n=224), mean age 75	Consistency of recommendations with evidence-based guides DRPs[a]	94% of pharmacists' recommendations were in accordance with evidence-based guides
Krass and Smith 2000	Phase I: Retrospective analysis of HMR case reports (completed by 45 pharmacists during HMR training) Follow-up by a GP survey after 3 months	Community-dwelling patients selected by 12 GPs (n=105), age not stated	Pharmacists' findings and recommendations[a] Change in mean number of drugs Medication costs	Decrease in number of drugs (7.4 vs. 6.5; p<0.001) Mean medication cost saving of AUD 19/month, corresponding of annual safe of AUD 229 (p<0.005)

Reference	Study design/method	Study population	Outcome measures	Key findings
Krass and Smith 2000	Phase II: Retrospective analysis of HMR case reports (completed by 35 pharmacists after HMR training) Follow-up after 3 months	Community-dwelling patients selected by 22 GPs (n=170), mean age 71 years	Pharmacists' findings and recommendations[a] Mean number of drugs Medication costs Clinical significance of resulting medication changes (subset of 141 cases)	Decrease in mean number of drugs (8.5 vs. 7; $p<0.001$) Mean medication cost saving of AUD 22/month, corresponding to annual saving of AUD 262 ($p<0.001$) 40% of actual medication changes (of the 103 reviews with actual medication changes) would result in significant positive effect on patient's health.
Nissen and Tett 2002*	RCT (12 month follow-up) (Costs 12 months before and after HMR)	Rural patients with e.g., ≥5 medications (n=88 interventions, 82 controls), mean age 70 years	Pharmacists' interventions HRQoL (SF-36, QWB) Cost-effectiveness (Pharmaceutical and Medical Benefit Scheme service costs)	91% of interventions evidence based. Physicians adopted 61% of interventions. No improvement in HRQoL Annual costs per patient rose AUD 1411 less compared to controls (AUD 931 vs. AUD 2 342)
Quirke et al. 2006	Retrospective analysis of HMR case notes, semi-structured telephone interview of HMR patients	All HMR cases (n=49) of one GP clinic, median age 63 years	Number of medication changes Patients' (n=44) and pharmacists' (n=4) opinions on HMR	84% of patients had changes made to medications by GP (33%: 1 change, 37%: 2, 14%: 3) All patients felt comfortable having pharmacist in their home, 20% reported discarding a medication and 25% taking medications differently after HMR. Pharmacists indicated better communication with patients and GPs.
Roughead et al. 2009	Retrospective cohort (administrative claims data, Jan 2004–July 2006)	Veterans aged ≥65 receiving β-blocker for heart failure (n=273 exposed to HMR, n=5 444 controls), mean age 82	Time to next hospitalization for heart failure	45% reduction in rate of hospitalization for heart failure at any time (HR 0.55) among patients that had received HMR.

Reference	Study design/method	Study population	Outcome measures	Key findings
Roughead et al. 2011	Retrospective cohort (administrative claims data Jan 2004–July 2006)	Ambulatory veterans, war widows and their dependents aged ≥65 dispensed warfarin (n=816 exposed to HMR, n=16 320 controls), mean age 81 years	Time to next hospitalization for bleeding	79% reduction in likelihood of hospitalization for bleeding between 2 and 6 months (HR 0.21) among patients that had received HMR. No difference in the time period from review to 2 months or in time period 6–12 months post HMR.
Sorensen et al. 2004	RCT 6-month follow-up (for costs 8 months)	Community-dwelling people aged 37–100 years (mean age 72), (n=400, follow-up available for 106/177 intervention and 196/223 control patients) 27 intervention GPs and 32 pharmacists	HRQoL physical and mental component (SF-36) Physician- and self-reported ADEs Number of GP visits, use of hospital services Severity of illness Participant satisfaction Drug and health service costs DRPs[a]	HMR improved the care of participants according to 92% of physicians and 94% of pharmacists. 97% of patients reported benefiting from participation. Physician-reported percentage of patients experiencing an ADE decreased in intervention group (37% vs. 9%), no change in the control group. No difference in HRQoL, use of hospital services, self-reported ADEs, severity of illness scores, number of GP visits or cumulative medication costs Adjusted net cost saving AUD 54/patient
Stafford et al. 2011	Observational cohort (analysis of HMR documentation submitted by 149 pharmacists)	Community-dwelling people aged 30–98 years (mean age 76), (n=661, data for drug cost analysis available for 560)	DRPs[a] Drug costs (at the time of HMR vs. after changes) Clinical outcomes: Avoided hospital days, GP and/or specialist consultations, and medical investigations (as estimated by an expert panel, random sample of 180 cases) Effect of assumed clinical outcomes on QoL and costs paid by the health system	Monthly drug cost saving AUD 1.7/patient Average avoided health care use/costs per patient/year: 0.065 hospital days / saving AUD 65 0.63 GP visits / saving AUD 21 0.16 specialist visits / saving AUD 11 Savings in medical investigations AUD 12 Savings in drug costs AUD 20 Total savings (AUD 128) do not cover the cost of HMR (AUD 329) Average gain in quality of life 0.003 QALYs

Reference	Study design/method	Study population	Outcome measures	Key findings
Urbis Keys Young 2005*	Telephone (n=50) and face-to-face (n=7) interviews after HMR (both before and after results collected retrospectively)	Patients receiving HMR in previous 3–12 months (n=57), 79% aged ≥65 years	HRQoL (EQ-5D) Number of patients reporting a medication-related event (hospital admissions, hospital stays, ED visits, GP visits, specialist visits, number of days off work, days unable to do usual tasks at home, days off work by carer) in the past 2 years vs. after HMR Consumer opinions and attitudes	Mean HRQoL utility score improved (0.562 vs. 0.681; $p<0.001$), most responsive attributes anxiety/depression and pain. More patients reported having a medication-related event before than after HMR: hospital admission (4 vs. 0); hospital stay (3 vs. 0); ED visit (3 vs. 0); GP visit (5 vs. 2); specialist visit (3 vs. 0); unable to do usual tasks at home (6 vs. 0); days off work by carer (1 vs. 0). No change in days off work (0 vs. 0). No statistical analyses. 21% of patients reported reduced symptoms or side effects after HMR. 44% indicated reassurance and improved confidence in relation to medications. 98% satisfied or very satisfied with HMR.

[a] Results regarding DRPs are presented in Table 11.

AACP=Australian Association of Consultant Pharmacy, ADE=Adverse drug event, DRP=Drug-related problem, ED=Emergency department, GP=General practitioner, HR=Hazard ratio, HRQoL=Health-related quality of life, MAI=Medication Appropriateness Index (Hanlon et al. 1992), PIM=Potentially inappropriate medication (Fick et al. 2003), QALY=Quality-adjusted life year, QWB=Quality of wellbeing, RCT=Randomized controlled trial

3 Drug-Related Problems (DRPs) in Pharmaceutical Care

Pharmaceutical Care and related medication review services aim at recognition, prevention and resolution of drug-related problems (DRPs). DRPs were defined by Strand and colleagues in 1990 (Strand et al. 1990) as “an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome” (Strand et al. 1990). Later, they used the term drug-therapy problem (DTP) and changed the definition to refer with DTP to “Any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with desired health outcomes” (Cipolle et al. 1998, 2004).

The pioneering work by the Strand’s research group stimulated other researchers to develop their own definitions and classification systems for DRPs. DRPs have grown to become a special area of clinical pharmacy research. The definitions and terminology related to DRPs are still far from uniform. In addition to the terms DRP and DTP, corresponding terms of medicine-related problem and medication-related problem have been used (Fernandez-Llimos et al. 2005). Also definitions differ from the ones by Stand et al. (1990) and Cipolle et al. (1998, 2004) by placing less emphasis on the patient’s experience. For example, according to the Pharmaceutical Care Network Europe (PCNE) DRP is “an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes” (PCNE 2010). Sometimes a very non-clinical approach has been taken, and a DRP has been defined as ”any problem that impacts on the patients’ ability to manage or take their medicines effectively” (Gordon et al. 2004). Fernandez-Llimos and colleagues (2005) have even suggested that the term DRP should be replaced with a term “negative clinical outcome”. This suggestion, however, prevents recognition and classification of potential problems and risks, the recognition of which is important in pharmaceutical care and medication review.

3.1 Systems to Classify DRPs

Numerous systems for classifying DRPs have been created in different countries to be used for the purposes of pharmaceutical care and research (van Mil et al. 2004). An optimal system should be validated, have a clear definition for DRPs in general and for each individual DRP category, be usable in practice, have a hierarchical structure and separate the problem from its cause and preferably also have an intervention section (van Mil et al. 2004). Based on a review by van Mil and colleagues (2004), no DRP classification meets all these requirements. Closest to an optimal classification system is the PCNE classification for DRPs (van Mil et al. 2004).

In this literature review, three classifications are described in detail because they were selected to be applied in the Finnish CMR procedure (see Chapter 6.2.4). These are Cipolle-Morley-Strand Classification, Westerlund classification and Pharmaceutical Care Network Europe classification.

3.1.1 Cipolle-Morley-Strand (CMS) Classification

The first systematic categorization for DRPs was published by Strand et al. in 1990 in order to focus the role of the pharmacist on patient needs and patient outcomes. According to their definition, "a DRP is an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome." In order for a DRP to exist, two conditions must be met: 1) a patient experiences or is likely to experience a disease or a symptom; and 2) this condition has actual or suspected relationship with drug therapy. Based on the above mentioned definitions, Strand and colleagues concluded that the number of DRPs is limited. As a result, their original DRP classification consisted of 8 DRP categories (Table 6). The authors emphasized that all DRPs can be either actual problems experienced by the patient or potential problems that may be prevented (Strand et al. 1990).

The classification was later revised by renaming DRPs as DTPs and by removing interactions, because they were considered merely as causes for DRPs. The remaining 7 DTPs were grouped around 4 drug-related patient needs: 1) indication; 2) effectiveness; 3) safety; and 4) compliance (Cipolle et al. 1998, Cipolle et al. 2004; Table 6). A definition for each DRP is available (Cipolle et al. 2004; Table 6). In the published versions of the "Cipolle-Morley-Strand (CMS) Classification" causes of DTPs are not categorized, but they need to be identified in order to solve the problem (Cipolle et al. 2004). However, a computer-based documentation system/software (Assurance Pharmaceutical Care™) to support the practice of pharmaceutical care includes both DTPs and several causes for each type of DTP (Table 6), as well as an intervention section (Medication Management Systems Inc. 2011). In addition, the system allows documentation of clinical patient outcomes and estimated cost savings in regard to use of other health care resources.

The CMS classification has been used in numerous studies to evaluate pharmacists' medication review services, mainly in the US (Isetts et al. 2003, Becker et al. 2004, Rao et al. 2007, Isetts at el. 2008, Ramalho de Oliveira et al. 2010, Angley et al. 2011). Various modifications of the classification have also been used in published studies (Ellis et al. 2000b, Roughead et al. 2004, Sorensen et al. 2004).

Table 6. *DRP/DTP classes and their definitions in the evolution of Cipolle-Morley-Strand classification (Strand et al. 1990, Cipolle et al. 1998, 2004)*

Strand et al. (1990)	**Cipolle et al. (1998, 2004)**		
DRP and definition	**Drug-related need**	**DTP and definition**	**Examples of causes for DTPs**
Untreated indications The patient has a medical condition that requires drug therapy but is not receiving a drug for that indication.	INDICATION	**Need for additional drug therapy** Additional drug therapy is required to treat or prevent a medical condition or illness from developing	Untreated condition Preventive therapy required Additional synergistic therapy needed
Drug use without indication The patient has a medical condition that is the result of taking a drug for which there is no valid medical indication.		**Unnecessary drug therapy** The drug therapy is unnecessary because the patient does not have a medical indication at this time.	No valid medical indication Duplicative therapy Non-drug therapy more appropriate
Improper drug selection The patient has a medical condition for which a wrong drug is being taken.	EFFECTIVENESS	**Ineffective drug** ('Wrong drug' in 1998) The product is not being effective at producing the desired response.	More effective drug available Condition refractory to drug Dosage form inappropriate
Subtherapeutic dosage The patient has a medical condition for which too little of the correct drug is being taken.		**Dosage too low** The dosage is too low to produce the desired response.	Dose too low Drug interaction Duration of therapy too short
Adverse drug reactions The patient has a medical condition resulting from an adverse drug reaction.	SAFETY	**Adverse drug reaction** The drug is causing an adverse reaction.	Unsafe drug for patient Drug interaction Allergic reaction
Overdosage The patient has a medical condition for which too much of the correct drug is being taken.		**Dosage too high** The dosage is too high, resulting in undesirable effects.	Dose too high Dosing frequency too short Dose administered too rapidly
Failure to receive drugs The patient has a medical condition that is the result of not receiving the prescribed drug.	COMPLIANCE	**Noncompliance** ('Adherence problem' in 1998) The patient is not able or willing to take the drug therapy as intended.	Instructions not understood Patient forgets to take the drug Drug product too expensive
Drug interactions The patient has a medical condition resulting from a drug-drug/food/laboratory interaction.			
Note: The DRPs are presented in a different order than in the original article (Strand et al. 1990) in order to ease comparison of the versions.			

3.1.2 Westerlund Classification

The DRP classification by Westerlund was developed in Sweden as a part of his PhD dissertation (Westerlund 2002). The aim was to create a system that could be used in community pharmacies during patient encounters to document DRPs and pharmacists' interventions. The classification was originally based on a definition in which a DRP is "a circumstance of drug therapy that may interfere with a desired therapeutic objective." Compared to the definition by Strand and colleagues (1990), the selected definition places less emphasis on actual patient experience, and was selected to reflect the inability of patients to always understand the circumstances that may interfere with therapeutic outcomes. Currently, the Westerlund classification relies on the DRP definition "A drug-related problem is a circumstance related to a patient/customer's use of a drug that actually or potentially prevents the patient from gaining the intended benefit of the drug (van Mil et al. 2004, Björkman et al. 2008). Definitions for each DRP category are also available (Westerlund 2002).

In the first phase of development Westerlund used his own professional experience to list 20 different options for problem types (Westerlund et al. 1999a). Four of these options were adopted from the DRP classification by Strand et al. (1990). The list was piloted by personnel from 12 pharmacies in Helsingborg, Sweden who were asked to categorize and tally the types of problems they identified during one week (Westerlund et al. 1999a). After piloting, some problem categories were merged or omitted. In addition, the development included discussions with Swedish and US colleagues who had experience with DRPs. The pilot phase and these discussions resulted in a 14-point DRP classification and an 11-point intervention classification (Westerlund et al. 1999a,b; Tables 7 and 8). Because of the used definition for DRPs, the Westerlund classification includes issues like DDIs and contraindications, which are considered to be causes of DRPs in many other classification systems (Consensus Committee 2002, PCNE 2010).

Since its development, the Westerlund classification has been updated four times (Tables 7 and 8). Version 2 was developed specially for documenting DRPs identified in customers purchasing OTC drugs, and related interventions (Westerlund et al. 2001). A computerized system for documenting DRPs and pharmacists' interventions in Swedish community pharmacies, SWE-DRP, was introduced in 2004 and is applied both to prescription and OTC customers (Westerlund and Björk 2006). Between April 2004 and September 2005 as much as 283 826 DRPs were documented in the database (Westerlund and Björk 2006). The computerized documentation of DRPs has been well accepted by community pharmacists, and so far, more than 1 million DRPs have been documented altogether (Westerlund 2009). In addition, the Westerlund system has been used in numerous studies in community pharmacy settings both to assess DRPs in prescriptions and OTC purchases (Westerlund et al. 1999a,b).

Table 7. *Evolution of DRPs in the Westerlund DRP classification system*

Version 1 (Westerlund et al. 1999a,b)	**Version 2** (Westerlund et al. 2001)	**Version 3** (van Mil et al. 2004)	**Version 4** (Ax et al. 2010)	**Version 5** (Westerlund 2009)
Uncertainty/lack of knowledge of the aim/function of drug	Uncertainty about the indication for the drug	Uncertainty about aim of the drug	=	=
Underuse of medication	=	=	=	=
Overuse of medication	=	=	=	=
Other dosage problem	=	=	-	-
Drug duplication	-	Drug duplication	=	=
Drug-drug interaction	=	=	Interaction	=
Therapy failure	=	=	=	=
Side effect	Adverse effect	=	Adverse reaction	=
Difficulty swallowing tablet/capsule	=	=	-	-
Difficulty opening container	=	=	=	-
Other practical problem	=	Other problem of administration/handling	Problem administering the drug	Practical problem
Language deficiency/ understanding disability	Language deficiency	-	-	-
Prescribing error	-	-	-	-
Other DRP	=	=	=	=
	Contraindication	=	=	=
			Inappropriate storage	-
			Inappropriate time / wrong dosing interval	=

= the definition remains the same as in the previous version. Note: The order of DRPs can be different from original publications in order to ease comparison of the different versions. All changes in wording between different Swedish versions are not evident in English translations.

Table 8. *Evolution of interventions to solve DRPS in the Westerlund DRP classification system*

Version 1 (Westerlund et al. 1999b)	**Version 2** (Westerlund et al. 2001)	**Version 3** (Montgomery et al. 2008)	**Version 4** (Westerlund and Björk 2006)	**Version 5** (Westerlund 2009)
No intervention	=	No intervention (explain)	=	-
Patient medication counseling	Customer drug counseling	Patient counseling	=	=
Practical instruction to patient	=	=	=	=
Patient referred to prescriber	=	Referral to prescriber or other health care provider	=	=
Prescriber informed only	-			
Prescriber asked for information or intervention	-	Contact with prescriber/ other healthcare provider	=	=
Intervention proposed by pharmacy, approved by prescriber	-	-	-	-
Intervention proposed by pharmacy, disapproved by prescriber	-	-	-	-
Switch of drug to _____	Switch of drug	=	=	=
Referral to colleague	=	-	-	-
Other intervention_____	=	Other intervention (explain)	Other intervention	=
		Printed information	=	=
			Information to patient's representative	=

= the definition remains the same as in the previous version. Note: The order of the interventions can be different from original publications in order to ease comparison of the different versions. All changes in wording between different Swedish versions are not evident in English translations.

3.1.3 Pharmaceutical Care Network Europe Classification

Pharmaceutical Care Network Europe (PCNE) was established in 1994 by European researchers on pharmaceutical care (www.pcne.org). In 2009 an official PCNE working group on DRPs was established, although it has worked informally since 2001. The first PCNE DRP classification was developed during a PCNE working conference in 1999 (van Mil et al. 2004). The aim was to develop a standardized system that could be used in international studies and ensure comparable results. Since its development, the classification has been updated several times (www.pcne.org). Major changes in the PCNE-system were completed in a Working Symposium in 2009 when the version 6.01 was created (www.pcne.org). Until then, the new versions had been made compatible with the previous ones (e.g., Version 5.01 in Table 9) but the version 6.01 was a totally revised classification system: most issues previously classified as DRPs were classified as causes of DRPs (www.pcne.org; see latest version V6.2 in Appendix 1). In addition, the possibility to determine whether the DRP is actual or potential was added. Remarkably, version 6 also enables classification of issues related to inappropriate treatment costs (Appendix 1).

The PCNE DRP classification enables categorization of the causes of DRPs, the interventions resulting from the recognition of the DRP and the outcomes of interventions in addition to the classification of DRPs (Appendix 1). The structure of PCNE classification is hierarchical. This means that each DRP category has primary domains and more specific subdomains. A definition for each primary domain DRP is clearly stated.

According to the published studies, the PCNE classification version 5.00 has been used in the hospital setting and in nursing homes (Lampert et al. 2008, Brulhart and Wermeille 2011) and the version 5.01 in community pharmacies during dispensing (Eichenberger et al. 2010), in medication review clinics (Chan et al. 2012) and among diabetics (van Roozendaal and Krass 2009). In medication review clinics 5% of DRPs could not be classified according to the PCNE classification (Chan et al. 2012). Also in the hospital setting the classification lacked some DRP categories, e.g., improper time of drug taking related to meals and prescribing errors (Lampert et al. 2008). The usability also in the community pharmacy setting was not optimal, since the classification does not include technical drug-related problems, such as lack of relevant information in the prescription (Eichenberger et al. 2010). So far, no studies that have utilized the version 6 have been published.

Table 9. *PCNE Classification for DRPs version 5.01 (PCNE 2006)*

Primary domain	Code	Problem
1. Adverse reactions Patient suffers from an adverse drug event	P1.1 P1.2 P1.3	Side effect suffered (non-allergic) Side effect suffered (allergic) Toxic effects suffered
2. Drug choice problem Patient gets or is going to get a wrong (or no drug) drug for his/her disease and/or condition	P2.1 P2.2 P2.3 P2.4 P2.5 P2.6	Inappropriate drug (not most appropriate for indication) Inappropriate drug form (not most appropriate for indication) Inappropriate duplication of therapeutic group or active ingredient Contra-indication for drug (incl. pregnancy/breast feeding) No clear indication for drug use No drug prescribed but clear indication
3. Dosing problem Patient gets more or less than the amount of drug he/she requires	P3.1 P3.2 P3.3 P3.4	Drug dose too low or dosage regimen not frequent enough Drug dose too high or dosage regimen too frequent Duration of treatment too short Duration of treatment too long
4. Drug use problem Wrong or no drug taken/administered	P4.1 P4.2	Drug not taken/administered at all Wrong drug taken/administered
5. Interactions There is a manifest or potential drug-drug or drug-food interaction	P5.1 P5.2	Potential interaction Manifest interaction
6.Others	P6.1 P6.2 P6.3 P6.4	Patient dissatisfied with therapy despite taking drug(s) correctly Insufficient awareness of health and disease (possibly leading to future problems) Unclear complaints. Further clarification necessary. Therapy failure (reason unknown)

3.2 Research on DRPs During Medication Review

Numerous studies have investigated pharmacists' ability to recognize and resolve drug-related problems during medication review. Such studies have been conducted in several countries both in the hospital (Cunningham et al. 1997, Blix et al. 2004, Blix et al. 2006, Mannheimer et al. 2006, Lampert et al. 2008), aged care home (Finkers et al. 2007, Nishtala et al. 2011) and outpatient settings (Kassam et al. 2001, Krska et al. 2001, Gilbert et al. 2002, Doucette et al. 2005). Medication review models in different countries are diverse in nature and many are not comparable to the Finnish CMR in their comprehensiveness. Because the MTM model in the US and the HMR in Australia were used as examples when the Finnish CMR model was developed, this literature review focuses on DRP studies conducted in these two settings. MTM studies are included if the intervention includes the 5 core elements of MTM service model (APhA and NADCS 2008) or complies with the principles of pharmaceutical care (Cipolle et al. 2004; Chapter 2.1.1). According to the focus of this dissertation, only studies involving outpatients are included. Disease-specific interventions are excluded.

3.2.1 DRPs in MTM

A large number of studies have investigated the DRPs pharmacists document and report to physicians during MTM (Table 10). Patient inclusion criteria in various studies differ, but usually include at risk patients with multiple medications and/or conditions or with specific disease states (Table 10). None of the retrieved studies included only patients aged ≥65 years. As a result, studies with at least some proportion of elderly patients are included.

The CMS DRP system has been used in almost all included studies to classify DRPs (Table 10). This simplifies the comparison of results between studies. On the other hand, the number of MTM encounters/patient has varied greatly in different studies, being as many as 9 in some studies (McDonough and Doucette 2003). This complicates comparison of the results because the reported mean number of DRPs per patient may represent pharmacists' findings after a single visit or over a period of time, of up to two years (Table 10).

In studies where the number of DRPs per encounter has been reported, the mean number of DRPs per patient has varied from 1.0 to 3.6 (Table 10). As an exception, one study reported an average of 9.9 problems/patient (Lewis et al. 2008). The results of this study are not comparable with the others, as common health-related problems, such as need for monitoring or lifestyle changes, were included in the analysis. If such issues are excluded, the mean number of problems per patient decreases to 5.4. The high prevalence of DRPs may result from the high number of drugs used per patient (mean 12.6) as the number of DRPs has been found to correlate with the number of drugs taken (Krska et al. 2001, Blix et al. 2004, Viktil et al. 2007, Stafford et al. 2009). The mean duration of MTM visits are rarely reported, but they can last as little as 5 to 15 minutes (Ellis et al. 2000b). This could provide one possible explanation for

different mean numbers of DRPs in different studies, as the length of patient visit affects the number of problems addressed and resolved (Ellis et al. 2000b).

In studies where the total number of DRPs during several MTM visits has been documented, the total number per patient has varied from 3.3 to 10.4 (Table 10). In the study with the highest prevalence of DRPs (Smith et al. 2011), the patients used higher mean number of drugs per person (15.7) compared to other studies (4.5–12.4) and the pharmacists had full access to patient medical records, which may have affected the results. The number of DRPs per single MTM encounter (1.0–3.6) is relatively low compared to the total number of DRPs per patient (3.3–10.4). This may reflect the continuous nature of the MTM procedure; the pharmacist does not have to address or report all issues after the first patient encounter, because several follow-up visits can be scheduled. Among patients with a large number of different medications (Smith et al. 2011) the pharmacists are likely to find new DRPs to be addressed during subsequent MTM encounters.

Across studies, the most common occurring DRPs during MTM have been similar (Table 10). In almost all studies reviewed the need for additional drug therapy is among the three most common DRPs (i.e., the patient has diagnosis, but not medication for that condition). Also poor adherence and too low drug doses have been common in most studies. Against these findings, it is not surprising that MTM has resulted in improved therapeutic patient outcomes in several studies (Chapter 2.2.1, Table 4). Interestingly, in the three studies where the mean number of DRPs was the highest (Ellis et al. 2000b, Doucette et al. 2005, Smith et al. 2011), poor adherence and need for education were the most common DRPs. The reason for this is not clear, but it is possible that the pharmacists in the other studies have prioritized clinical findings and underreported patient-related adherence issues.

Few MTM studies have indicated what drugs are most commonly involved in DRPs reported by pharmacists (Table 10). Asthma medications and cardiovascular drugs have been frequently mentioned in such studies (Strand et al. 2004, Doucette et al. 2005, Ramalho de Oliveira et al. 2010, Smith et al. 2011). Undertreatment, i.e., need for additional therapy and use of too low doses, has involved especially salicylates, calcium supplements, antidiabetics, ACE-inhibitors and statins (Strand et al. 2004, Rao et al. 2007, Ramalho de Oliveira et al. 2010). Statins and ACE inhibitors have also been involved in poor adherence (Strand et al. 2004, Ramalho de Oliveira et al. 2010).

Table 10. *Summary of studies on drug-related problems (DRPs) identified during Medication Therapy Management (MTM). Presented in alphabetical order.*

Reference State	Population	n	Mean age, years (range)	No of drugs, mean	DRP classification system	No of DRPs, mean	Most common DRPs (% of DRPs unless otherwise stated)	Drugs commonly involved in DRPs (% of drugs)
Becker et al. 2004 Iowa	Medicaid enrollees	754 care plans	54.9	NS	CMS 1998	NS	ADR (20.1% of care plans) Need for additional drug therapy (18.9%) Lack of adherence (16.3%)	NS
Chrischilles et al. 2004 Iowa	Medicaid enrollees, ≥4 medications	203	54.1, 28% aged ≥65	7.5	NS	2.6 (several visits)	Untreated condition (17.6% of recommendations) Therapeutic monitoring needed (16.7%)	NS
Christensen et al. 2007 North Carolina	State health plan enrollees with poly-pharmacy	67	68, 60% aged ≥65	41 pre-scrip-tions/6 months	NS	3.6 (at initial visit)	Potential underuse (71.6% of patients) More cost-effective drug available (64.2%) Suboptimal drug (53.7%)	NS
Doucette et al. 2005 Iowa	Medicaid recipients, ≥4 medications, 1 of 12 conditions	150	54.4 (7–93)	9.3	Identical to CMS 1998	5.9 (several visits during 2 years)	Inappropriate adherence (25.9%) Need for additional therapy (22.0%) Wrong drug (13.2%)	Respiratory agents (17.7% of DRPs) Cardiovascular (15.5%) Analgesics (14.4%) CNS agents (14.3%)
Ellis et al. 2000b Multicenter	Veterans affairs medical centers patients, ≥3 of 6 criteria e.g., ≥5 drugs, ≥3 diseases)	523	67	NS	Modified Hepler and Strand (1990)	5.8 (during 1 year, 1.6/visit)	Requires drug therapy education (32.7%) Needs a drug but is not receiving it (16.0%) Not taking a drug as prescribed (14.3%)	NS

Reference State	Population	n	Mean age, years (range)	No of drugs, mean	DRP classification system	No of DRPs, mean	Most common DRPs (% of DRPs unless otherwise stated)	Drugs commonly involved in DRPs (% of drugs)
Farris et al. 2004 Iowa	Medicare enrollees	1167	77	5	NS	1.7 (1 time review)	DDI (35.0%) Duplication (16.4%) Indication but no drug (15.7%)	Vitamins and minerals, ACE-inhibitors, salicylates (%NS)
Fischer et al. 2002 Minnesota	HMO en-rollees, heart or lung disease	231	57	9.1	CMS, excluding adherence	NS	Dose too low (34% of patients) ADR (34%) Needs additional drug therapy (25%)	NS
Isetts et al. 2003 Minnesota	Fairview health service clinic patients	2524	NS (3–97), 48% aged ≥65	8.2	CMS	2.3 (mean 2.3 visits)	Need for additional therapy (29%) Dosage too low (22%) Adherence (18%)	
Isetts et al. 2008 Minnesota	Fairview health service clinic patients, ≥1 of 12 conditions	285	NS, 14% aged ≥65	7.9	CMS	2.2 (during 1 year)	Additional drug therapy needed (33.9%) Dose too low (19.9%) ADR (14.1%)	NS
Lewis et al. 2008 Michigan	Patients taking ≥4 drugs for chronic diseases	67	68.7, 60% aged ≥65	12.6	Modified Tomechko et al. (1995)	9.9	Need for additional drug therapy monitoring (29.2%) Need for lifestyle change (15.7%) Need for actions to avoid ADE (12.7%)	
McDonough and Doucette 2003 Iowa	Hyperlipidemia patients	116	55.3 (29–82)	4.5	CMS	4.4 (during 2 years, mean 9 visits)	Needs additional therapy (39.8%) Nonadherence (31.1%) ADR (11.7%)	

Reference State	Population	n	Mean age, years (range)	No of drugs, mean	DRP classification system	No of DRPs, mean	Most common DRPs (% of DRPs unless otherwise stated)	Drugs commonly involved in DRPs (% of drugs)
Moczygemba et al. 2011 Virginia	Homeless patients of a mental health clinic or a medical clinic, ≥1 chronic disease, ≥2 chronic drugs	209 mental health, 40 medical clinic	NS	NS	NS	2 5.1	Mental health clinic: Ineffective drug therapy (27.1%) Need for education (26.8%) Nonadherence (25.9%) Medical clinic: Need for education (59.5%) Nonadherence (19.0%) Need additional drug therapy (9.8%)	NS
Rao et al. 2007 Minnesota	Patients in community pharmacies and ambulatory clinics	1598	68 (40–100)	6	CMS 1998	2.3 (during 1 year)	Needs additional drug therapy (32%) Dose too low (23%) Non-compliance (16%)	DRP-drug combinations: Salicylates/needs additional therapy (3.6%) Calcium/needs additional therapy (3.1%) Anticoagulants/dose too low (2.8%)
Ramalho de Oliveira et al. 2010	Fairview MTM enrollees aged ≥21	9068	NS, (21–100), 45% aged ≥65	12.4	CMS	4.2 (mean 3.7 visits)	Needs additional drug therapy (28.1%) Dose too low (26.1%) Nonadherence (16.5%)	Needs additional: ASA, Ca, statins, antidiabetics Dose low: Ca, antidiabetics, statins, ACE inhibitors Nonadherence: statins, antidiabetics, PPIs, ACE-inhibitors
Smith et al. 2011 Connecticut	Adult Medicaid beneficiaries, ≥1 chronic conditions, ≥3 chronic drugs	88	51	15.7	CMS 2004	10.4 (mean 4.6 visits/1 year)	Adherence (26.2%) Needs additional drug (22.7%) Dose too low (16.3%)	Antidiabetics Analgesics (NSAIDs and opioids) Asthma and COPD medications

Reference State	Population	n	Mean age, years (range)	No of drugs, mean	DRP classification system	No of DRPs, mean	Most common DRPs (% of DRPs unless otherwise stated)	Drugs commonly involved in DRPs (% of drugs)
Strand et al. 2004 Minnesota	Adult patients	2985	NS (18–100), 52% aged ≥65	8	CMS	3.3 (during≥ 2 visits) (1.1 during first visit)	Needs additional drug therapy (30.6%) Dosage too low (21.2%) Noncompliance (18.4%)	Low dose: Ca, statins, ACE-inhibitors, insulin, warfarin, betablockers High dose: salicylates, warfarin, Ca, insulin, thyroid hormones ADR: statins, ASA, SSRIs, NSAIDs, ACE-inhibitors Adherence: statins, steroid inhalants, ACE-inhibitors, PPIs
Triller et al. 2003 New York	Home care patients with one of 6 criteria (e.g., falls, ≥10 medications)	80	NS	NS	CMS 1998	3.4	Need for additional therapy (20%) Wrong drug therapy (18%) Poor compliance (17%)	NS
Welch et al. 2009 Colorado	Medicare enrollees, ≥2 chronic conditions, ≥5 medications, predicted drug costs >USD 4000/year	459	68.8	NS (≥5)	NS	NS	DDI (52.7% of patients) Nonadherence (34.4%) Dose adjustment (26.6%)	NS

ADR=Adverse drug reaction, Ca=Calcium supplement, CMS=Cipolle-Morley-Strand (Cipolle et al. 2004), DDI=Drug-drug interaction, HMO=Health maintenance organization, NS=Not stated, NSAID=Non-steroidal anti-inflammatory drug, PPI=Proton pump inhibitor, SSRI=Serotonin-selective reuptake inhibitor

3.2.2 DRPs in HMR

Several studies have investigated the DRPs pharmacist report during HMR (Table 11). Even though all patients in these studies have not been aged, the mean or median age has been high; 66–76 years. Thus, all studies found have been included in this chapter.

Interpretation and comparison of DRP studies during HMR should take into account that there is variation between the DRP classification systems used and ways of reporting the results. For example, at least three published studies have used the same 1000 HMR case reports, but have reported inconsistent results (Gilbert et al. 2002, Roughead et al. 2004, Rao et al. 2007). Gilbert et al. (2002) and Roughead et al. (2004) used a modified CMS classification and found the mean number of DRPs per person to be 2.8 and 2.2, respectively. Rao et al. (2007) selected 982 patients aged ≥40 years from the same HMR case reports and reported mean number of 2.1 DRPs/person by using the original CMS classification. Likewise, the most common DRP classes differed between these studies (Table 11). Gilbert et al. (2002) reported "Need for additional test" to be the most common DRP (17.5% of DRPs). As lack of monitoring is not regarded as a DRP in the original CMS classification used in the study by Rao et al. (2007), they stated "non-compliance" to be clearly the most common DTP (31.7%). Roughead et al. (2004), on the other hand, used a different method of presenting results and reported most common DRPs as percentages of patients experiencing them (Table 11).

Overall, the mean number of DRPs per patient during HMR has varied from 2.1 to 9.7 (Table 11). In contrast to MTM studies from USA with varying number of encounters, in these studies DRPs were reported after a single HMR patient visit. The number of DRPs has been found to correlate with the number of medications taken (Krska et al. 2001, Blix et al. 2004, Viktil et al. 2007, Stafford et al. 2009). In HMR studies the mean number of drugs used has been high (7.4–11.8). Still, the HMR studies with highest mean number of drugs do not report the highest mean number of DRPs (Table 11). Also, there is no indication that higher age is associated with higher number of DRPs (Stafford et al. 2009; Table 11). Instead, number of DRPs seems to be affected by the DRP classification system used as the studies with the lowest mean number of DRPs have utilized the original or modified CMS DRP-classification system for analysis (Table 11). It is also possible that the prevalence of DRPs is affected by the patient population's clinical conditions. There is some evidence, that higher number of clinical conditions is associated with higher number of DRPs (Stafford et al. 2009). Also, the mean number of DRPs has been high among mental health patients (Bell et al. 2006).

The most frequent DRPs in most HMR studies have been similar, and related to patients' poor adherence or knowledge, ADRs, and need for additional medication (Table 11). Also drug interactions and need for additional tests or monitoring have been common. However, the DRP classification used affects the results as different coding systems have different number and type of DRP classes. Also, the involved patient populations may influence the results. ADRs seem to be more common among mental health patients (Bell et al. 2006) than among other patients (Table 11). On the

other hand, when HMR has involved cardiovascular patients recently discharged from hospital –a situation where drug regimen is likely to change- 'uncertainty about aim of drug' comprised a third of all DRPs (Ellitt et al. 2010).

Most common drugs involved in DRPs have been rarely reported in HMR studies (Table 11). The results differ, largely because they are presented on different Anatomic Therapeutic Chemical classification (ATC) levels. In the study by Roughead et al. (2004) most common drugs on ATC level 1 were cardiovascular drugs (26.3%), drugs affecting the nervous system (17.9%), and drugs affecting the alimentary tract (15.7%). Stafford et al. (2009) reported their complete results on ATC level 3. The most common drug groups involved in DRPs were NSAIDs (7.7%) and antithrombotic agents (6.9%) (Table 11). However, when counted from the 20 most common ATC level 3 drug groups presented (63.9% of all drugs), at ATC level 1 cardiovascular drugs caused at least 19.5% and nervous system drugs 15.5% of DRPs, being the most common drug groups like in the study by Roughead et al. (2004). Rao et al. (2004) used the same data as Roughead et al. (2004) but reported most common drugs involved in DRPs only in the form of five most common DRP-drug combinations. In contrast with other studies, this different way of reporting placed pneumococcal vaccines in combination with DRP 'need for additional therapy' as the most common. Regardless of the way of presenting the results, analgesic drugs are commonly involved in DRPs during HMR (Table 11). They are mentioned among the 3 most common drugs in 3 out of 4 studies in which the drugs are reported (Roughead et al. 2004, Rao et al. 2007, Stafford et al. 2009, Stafford et al. 2011).

Table 11. *Summary of studies on drug-related problems (DRPs) identified during Home Medicines Review (HMR). Presented in alphabetical order.*

Reference	n	Mean age, years (range)	No of drugs, mean	DRP classification system	No of DRPs, mean	Most common DRPs (% of DRPs unless otherwise stated)	Drugs commonly involved in DRPs (% of drugs)
Bell et al. 2006[a]	49	66 (21–87)	9.1	Adapted Clinical Pharmacy Activity Classification System (Jones and Whitehead 2004)	8.2	Suspected or potential ADR (25.1%) Potential interactions (7.4 %) Patient taking additional drug (6.4%)	NS
Castelino et al. 2011	224	74.6 (65–96)	10.7	Modified CMS 1998	4.9	Need for additional medicine (16.1%) Investigation test requested (14.2%) Rationalization of drug therapy (11.1%)	NS
Ellitt et al. 2010[b]	76	66.0 (32–88)	10.8	Westerlund version 4	5.2	Uncertainty about drug aim (32.0%) Potential interaction (22.4%) Adverse reaction (15.1%)	NS
Gilbert et al. 2002	1000	Median men 72, women 74 (1–100)	9	Modified CMS 1998	2.8	Need for additional test (17.5%) Need for additional medicine (11.6%) Wrong or inappropriate medicine (11.5%) (20% related to patient knowledge and skills, and adherence)	NS
Krass and Smith 2000 Phase I: during HMR training	105	NS	7.4	NS	7.7	Interactions (12.6%) Side effects (11.7%) More appropriate therapy available (6.4%)	NS
Phase II: after HMR training	170	71	8.5	NS	9.7	Query compliance (16.4%) Side effects (14.3%) Interactions (12.9%)	NS

Reference	n	Mean age, years (range)	No of drugs, mean	DRP classification system	No of DRPs, mean	Most common DRPs (% of DRPs unless otherwise stated)	Drugs commonly involved in DRPs (% of drugs)
Rao et al. 2007 (Data from Gilbert et al. 2002)	982	73 (40–100)	9	CMS 1998	2.1	Non-compliance (31.7%) Needs additional therapy (15.9%) Ineffective drug (15.7%)	DRP-drug combinations: Pneumococcal vaccines/ needs additional therapy (3.9% of DRPs) Paracetamol/dose low (3.5%) Salicylates/needs additional therapy (1.9%)
Roughead et al. 2004 (Data from Gilbert et al. 2002)	1000	Median men 74, women 75.5 (1–100)	9	Modified CMS	2.2	Need for additional test (33.4% of patients) Use of wrong or inappropriate medicine (26.8%) Need for additional medication (24.9)	Cardiovascular (26.3%) Nervous system (17.9%) Alimentary tract (15.7%)
Sorensen et al. 2004	110	72.3 (37–100)	9.1	Adapted Strand et al. 1990	5.5	ADR (16.9%) Suboptimal monitoring (16.3%) Adherence difficulties (12.8%)	NS
Stafford et al. 2009, Tenni et al. 2007	138	73.9 (45–94)	11.7	D.O.C.U.M.E.N.T (Peterson and Tenni 2004)	4.8	Drug selection (24.0%) Toxity, ADR or side-effect (19.0%) Untreated indications (16.6%)	NSAIDs (7.7%) Antithrombotic agents (6.9%) Antidepressants (6.7%)
Stafford et al. 2011	661	76.0 (30–98)	11.8	D.O.C.U.M.E.N.T (Peterson and Tenni 2004)	3.5	Untreated indications (27.5%) Drug selection (22.0%) Compliance and concordance (13.8%)	DRP-drug combinations: Analgesics/condition not adequately treated (6.4% of DRPs) Antithrombotics/DDI (3.1%) Renin-angiotensin system agents/DDI (2.7%)

[a] Patients with mental illness, [b] Recently discharged cardiovascular patients

ADR=Adverse drug reaction, CMS=Cipolle-Morley-Strand (Cipolle et al. 1998, 2004), DDI=Drug-drug interaction, NS=Not stated, NSAID=Non-steroidal anti-inflammatory drug

4 Potentially Inappropriate Prescribing Among the Aged

Aging involves impairment of functional reserve capacity and results in several physiologic, pharmacokinetic and pharmacodynamic alterations in the body that may increase the sensitivity of elderly people to drug effects and make them more vulnerable to adverse drug effects (Mangoni and Jackson 2004, ELDesoky 2007, Klotz 2009). Elderly patients also often have several concomitant clinical conditions which results in polypharmacy. In addition, the prevalence of polypharmacy increases with advancing age even if adjusted for comorbidity (Haider et al. 2009). Polypharmacy has several consequences in older people, including increased risk for ADRs and potentially serious DDIs but also undertreatment (Hanlon et al. 2006, Hilmer and Gnjidic 2009, Johnell et al. 2009). Excessive polypharmacy (i.e., use of 10 or more concomitant drugs) has been even associated with increased risk of death in patients aged over 80 years (Jyrkkä et al. 2009).

A significant number of ADEs, ADRs and relating hospitalizations among the elderly are preventable, i.e., resulting of suboptimal or inappropriate prescribing or monitoring (Beijer and de Blaey 2002, Gurwitz et al. 2003, van der Hooft et al. 2008a). Suboptimal or inappropriate prescribing may include underprescribing (failure to prescribe needed medications), overprescribing (prescribing more drugs than needed) and misprecribing (prescribing incorrectly a needed medication) (Hanlon et al. 2001, Spinewine et al. 2007).

As pharmacotherapy among the aged is challenging and may involve various risks, several criteria to identify inappropriate prescribing and drug use among elderly patients have been developed (Dimitrow et al. 2011). Usually, the development of the criteria has been based on literature reviews, clinical expertise of the researchers and/or on previous criteria (Dimitrow et al. 2011). Most of the criteria have been validated by using consensus methods, but some by using patient medical records.

The criteria to indicate inappropriate prescribing can be explicit which means that they are based on pre-determined standards, are usually drug- or disease-oriented, and can be easily applied without significant clinical judgment (Spinewine et al. 2007, Dimitrow at al. 2011). Because the explicit criteria are usually quite simple drug-to-avoid lists, they can only detect small fraction of prescribing problems and do not take into account the individual properties of patients (Spinewine et al. 2007, Steinman et al. 2009). As a result, they cannot be used alone as quality measures of prescribing or assessment of the appropriateness of individual patients' pharmacotherapy (Steinman et al. 2009). However, explicit tools are good for screening the appropriateness of prescribing from drug charts or large population databases.

Implicit tools and criteria, on the other hand, focus usually on the individual patient and clinical judgment is needed to assess the appropriateness of pharmacotherapy (Spinewine et al. 2007). Thus, they are more time-consuming to use and the results are easily affected by the clinical knowledge of the person using them (Spinewine et al. 2007). On the other hand, implicit criteria are not easily affected by national drug formularies and allow better transferability across countries (Dimitrow

et al. 2011). Whether implicit or explicit, good criteria should have an association with adverse health outcomes (Gallagher et al. 2007).

4.1 Explicit Criteria to Indicate Inappropriate Prescribing

4.1.1 The Beers Criteria and Their Derivatives

The most used tool to evaluate potentially inappropriate medication (PIM) use among older people is the Beers criteria, which were developed in the US by a consensus panel of experts in 1991 and updated twice since then (Beers et al. 1991, Beers 1997, Fick et al. 2003). In the Beers criteria drugs are judged as inappropriate if evidence of their effectiveness is lacking, if their adverse effects outweigh the benefits or if safer alternatives exist. In updates of the criteria inappropriate disease-drug combinations are also considered (Beers 1997, Fick et al. 2003). The first set of Beers criteria included 30 medications or categories of medications to be avoided in frail nursing home residents aged ≥65 years; 19 were considered as generally avoidable and 11 were considered avoidable based on dose, frequency or duration of treatment (Beers et al. 1991). In 1997 the criteria were updated to be used on all persons aged 65 and older regardless of frailty or place of residence (Beers 1997). The updated list included 28 criteria considering medications or medication categories to be avoided generally or depending on the daily dose, and 15 criteria on medications or classes of medications that should be avoided in 15 common disease states (Beers 1997). In 2001 Zhan et al. modified the Beers 1997 criteria by including only the drugs that were considered inappropriate irrespective of diagnoses or dose. They also used a modified Delphi method to categorize the 33 drugs into 3 categories i.e., “should always be avoided”, “are rarely appropriate” and “have some indications but are often misused” (Zhan et al. 2001).

The latest update of the Beers criteria was published in 2003 (Fick et al. 2003). Several medications were added (n=44) and dropped (n=15), and as a result the final criteria consisted of 48 medications or medication classes to be avoided generally or based on dose or duration of treatment, and of 20 diseases or conditions and medications to be avoided with these conditions (Fick et al. 2003). The latest update also rates each criterion as having high or low severity. Of the 78 individual medications listed in the Beers 2003 criteria, 37 were marketed as oral preparations in Finland in 2007 (Table 12). Since then carisoprodol, dextropropoxyphene, disopyramide and oral piroxicam have been removed from the market in Finland.

Because the original Beers criteria do not take into account underprescribing, a refinement to the Beers criteria to state 13 preferred medications for 4 medical conditions was published in 2009 (Stefanacci et al. 2009). The preference of medications is based on thorough clinical evidence of their effectiveness and smaller risk compared to other alternative medications for that condition. The first set of the “positive Beers criteria” includes only 4 medical conditions affecting central nervous

system (dementia, depression, Parkinson's disease, and psychosis), but there is an intention to expand the criteria with other conditions frequently encountered in older adults.

Because the Beers criteria are based on drug selection in the US, their transferability to other countries with different drug formularies is not optimal. As a result, several national modifications have been made and new criteria been developed. Most of these criteria are based on the Beers criteria (Dimitrow et al. 2011).

In Canada McLeod and colleagues used Delphi consensus method to create their own set of explicit criteria by using the Beers 1991 criteria as a foundation (McLeod et al. 1997). As a result, 38 inappropriate prescribing practices for people aged ≥65 years were identified. Eighteen drugs were considered as generally contraindicated, 16 criteria involved a drug-disease interaction, and 4 criteria a DDI. Another Canadian set of criteria, the Improved Prescribing in the Elderly Tool (IPET) was created by extracting the 14 most prevalent PIMs or drug-disease combinations from the McLeod criteria by using 361 inpatient charts in an acute care hospital in Ontario (Naugler et al. 2000). Only 2 drug groups: long-half life benzodiazepines and tricyclic antidepressants with active metabolites, were considered to be generally avoidable by persons aged 70 and older according to IPET (Naugler et al. 2000). The remaining 12 criteria consider inappropriate drug-disease combinations. The IPET is quite exclusive and weighted towards cardiovascular drugs (4 criteria), psychotropics (5) and NSAIDs (3).

In Europe the French used Delphi method to create a modified version of the 1997 Beers criteria by using also McLeod criteria as a foundation (Laroche et al. 2007a). The French criteria are based on national drug selection in France and consider drug groups rather than individual drugs when defining PIMs for people aged ≥75 years. As a result, the French criteria include several additional cerebral vasodilators and long-acting benzodiazepines (n=13) not found in the original Beers criteria. The French also added three new criteria: concomitant use of two (or more) NSAIDs, concomitant use of two (or more) psychotropic drugs form the same therapeutic class and use of any anticholinergic drug in addition to those listed in the Beers criteria (Laroche et al. 2006). The final French list consists of 34 criteria: 29 involve drugs or drug classes or drug combinations to be avoided generally, and 5 medications to be avoided in specific medical conditions.

An Italian expert panel refined the Beers 2003 criteria by excluding disease-specific criteria and several drugs from the original Beers 2003 diagnoses-independent list (Maio et al. 2010). Several drug groups, like long- and short-acting benzodiazepines, antihistamines and stimulant laxatives were deemed inappropriate by the expert panel but excluded from the PIM list because they were not reimbursable by the 2006 Italian National Formulary (Maio et al. 2010). Two criterion; atypical antipsychotics and oral NSAIDs for >15 days, were added. As a result, the Italian PIM criteria consist of 23 avoidable drugs or drug classes categorized similarly to the Zhan criteria (Zhan et al. 2001) as "always avoidable", "appropriate in certain circumstances" and "having some indications but are often

subject to inappropriate use". In addition to these explicit criteria, the Italians are currently developing CRIteria to assess appropriate Medication use among Elderly Complex patients (CRIME) by translating the recommendations of disease-specific clinical guidelines to elderly complex patients with limited life expectancy, functional and cognitive impairment and geriatric syndromes (Fusco et al. 2009). The criteria have not yet been published.

The Norwegians developed and validated a list of drugs and combinations of drugs to be avoided in patients aged ≥70 years in general practice; the Norwegian General Practice (NORGEP) criteria (Rognstad et al. 2009). The Beers criteria (Beers 1991, Beers et al. 1997, Fick et al. 2003), the Swedish quality indicators for elderly pharmacotherapy (Socialstyrelsen 2003) and earlier Norwegian studies and literature were used when developing the NORGEP criteria. The NORGEP criteria consist of a 36-item list, of which 21 are avoidable drugs or doses and 15 include avoidable drug combinations (Rognstad et al. 2009). Of the avoidable drug combinations 8 involve warfarin or NSAIDs. As in other PIM criteria, tricyclic antidepressants, long-acting benzodiazepines and first generation antihistamines were included.

The most recent European PIM list has been developed in Germany (Holt et al. 2010). The PRISCUS list was developed based on the Beers, McLeod and The French criteria and on the Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert doctors to the Right Treatment (START) -tool (Barry et al. 2007, Gallagher et al. 2008a), a literature review and an expert panel. The list consists of 18 drug classes including 83 drugs. Of these, 63 were also included in one or more of the originally used PIM lists. For all PIMs in the PRISCUS list, a possible therapeutic alternative is stated. For the cases in which the use of a PIM is considered necessary, the list contains precautions to be taken during the use, e.g., recommendations on monitoring.

A Japanese version of the Beers criteria was developed by a consensus method and includes 46 drugs/drug classes to generally be avoided in persons aged 65 and older (Akazawa et al. 2010). Of these, 15 were not included in the original Beers 2003 criteria. 25 conditions and drugs to be avoided with these conditions are also listed, 7 of which were not included in the Beers 2003 criteria.

Table 12. *Potentially inappropriate medications (PIMs) independent of diagnoses and conditions according to Beers 2003 criteria (modified from Fick et al. 2003) available for outpatient care in Finland in 2007.*

Drug	**Cause for inappropriateness**	**Severity (Low or high)**
(Dextro)propoxyphene	Few analgesic advantages over acetaminophen, yet the adverse effects of narcotic drugs.	Low
Indomethacin	Of all NSAIDs the most CNS adverse effects.	High
Muscle relaxants and antispasmodics: carisoprodol, short-acting oxybutynin	Poorly tolerated: cause anticholinergic adverse effects, sedation, and weakness. Effectiveness at tolerated doses questionable.	High
Amitriptyline, chlordiazepoxide-amitriptyline, perphenazine-amitriptyline	Strong anticholinergic and sedative properties, rarely the antidepressant of choice for elderly patients.	High
Doxepin	-‘’-	High
Meprobamate	Highly addictive and sedating anxiolytic.	High
Short-acting benzodiazepines: doses greater than lorazepam 3 mg; oxazepam 60 mg; alprazolam 2 mg; temazepam 15 mg; triazolam 0.25 mg	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums.	High
Long-acting benzodiazepines: diazepam,chlordiazepoxide, chlordiazepoxide-amitriptyline, clidinium-chlordiazepoxide	Prolonged sedation, increased risk for falls and fractures. Short- and intermediate-acting benzodiazepines are preferred.	High
Disopyramide	Potent negative inotrope, therefore may induce heart failure. Strongly anticholinergic. Other antiarrhythmics should be used.	High
Digoxin >0.125 mg (except for atrial arrhythmias)	Decreased renal clearance may lead to increased risk of toxic effects.	Low
Short-acting dipyridamole	May cause orthostatic hypotension.	Low
Gastrointestinal antispasmodic drugs: belladonna alkaloids, clidinium-chlordiazepoxide	Highly anticholinergic, uncertain effectiveness.	High
Anticholinergics and antihistamines: hydroxyzine, diphenhydramine, tripelennamine[a]	Anticholinergic properties.	High

Drug	Cause for inappropriateness	Severity (Low or high)
Diphenhydramine	May cause confusion and sedation. Should not be used as a hypnotic. When used to treat emergency allergic reactions, should be used in the smallest possible dose.	High
Ergot mesyloids	Not effective in the doses studied.	Low
Ferrous sulfate >325 mg/d	Absorbed amount not increased, but increased incidence of constipation.	Low
Ketorolac[b]	Immediate and long-term use should be avoided, since a significant number have asymptomatic GI pathologic conditions	High
Amphetamines and anorexic agents (dexamphetamine, modafinil, methylphenidate and sibutramine)	Potential for causing dependence, hypertension, angina, and myocardial infarction.	High
Long-term use of full-dosage, longer half-life non-COX-selective NSAIDs: naproxen, piroxicam	Risk for GI bleeding, renal failure, high blood pressure, and heart failure.	High
Daily fluoxetine	Long half-life, risk for excessive CNS stimulation, sleep disturbances, and increased agitation. Safer alternatives exist.	High
Long-term use of stimulant laxatives except in the presence of opiate analgesic use: bisacodyl	May exacerbate bowel dysfunction.	High
Amiodarone	QT interval problems, risk of provoking torsades de pointes. Lack of efficacy.	High
Orphenadrine	More sedative and anticholinergic than safer alternatives.	High
Nitrofurantoin	Potential to renal impairment. Safer alternatives available.	High
Short acting nifedipine	Potential for hypotension and constipation.	High
Clonidine	Potential for orthostatic hypotension and CNS adverse effects.	Low
Estrogens only (oral)	Evidence of the carcinogenic potential, lack of cardioprotective effect.	Low

[a] Available only as an ointment for insect bites. Not considered as a PIM.
[b] Available only as eye drops and as an injection for hospital use. Not considered as a PIM.
CNS=Central nervous system, GI=gastrointestinal, NSAID=non-steroidal anti-inflammatory drug

4.1.2 Criteria Independent of the Beers Criteria

In addition to not taking into account variations in national drug selections, the Beers criteria have been criticized for including several drugs that are nowadays rarely used, lack of structure in the presentation of criteria and omission of several important and common instances of prescribing, such as inappropriate under-utilization of drugs, DDIs and duplicate drug classes (O'Mahony and Gallagher 2008).

In Ireland evidence-based literature and experience of the researchers were used to develop a two-part tool to counter to the criticism of the Beers criteria and to take into account both inappropriate prescribing and underprescribing among persons aged 65 or older (Gallagher et al. 2008a). Screening Tool of Older Persons' Prescriptions (STOPP) has been validated for European setting to indicate 65 potentially inappropriate prescribing practices in older people (Gallagher et al. 2008a, Hamilton et al. 2009). The STOPP criteria are arranged according to physiological systems but also include criteria on analgesic drugs and on drugs that may adversely affect fallers, and a general statement to avoid duplicate drug classes. Most of the STOPP criteria concern inappropriate drug-disease combinations (n=42) or inappropriate duration of treatment (n=12). Of the remaining criteria 4 concern inappropriate drug combinations, 2 inappropriate doses, 3 non-indicated treatments and 2 need for combination/supplementary/additional therapy (Gallagher et al. 2008a). However, one criterion may contain several aspects of inappropriateness, for example inappropriate duration of treatment in certain disease states. The STOPP tool is designed to be used alongside with the Screening Tool to Alert doctors to the Right Treatment (START) -tool (Barry et al. 2007, Gallagher et al. 2008a) in order to address underprescribing. The START-tool consists of 22 common disease states found in the elderly (e.g., cardiovascular diseases and osteoporosis) and appropriate, indicated, evidence-based treatments for these conditions (Gallagher et al. 2008a).

In Ireland the STOPP tool identified significantly higher proportion of patients requiring hospitalization as a result of PIM-related adverse events than the Beers 2003 criteria (11.5% vs. 6%) and was concluded to be more sensitive in identifying patients who could be injured by inappropriate prescribing (Gallagher and O'Mahony 2008).

In Finland a national database on elderly pharmacotherapy by the Finnish Medicines Agency has been available since 2010 to support clinical decision making regarding pharmacotherapy of persons aged 75 and older, and to improve medication safety in primary care (Fimea 2011). The database consists of 350 drugs commonly used by elderly patients in Finland. Of these some are included because they are listed in the Beers criteria (Fick et al. 2003), the French criteria (Laroche et al. 2007) or in the quality indicators for drug use in elderly persons by the Swedish National Board of Health and Welfare (Socialstyrelsen 2003, Ahonen 2011, Fimea 2011). The drugs are classified in categories A–D based on the research literature and clinical knowledge of the experts involved in the development of the database. Class A drugs are appropriate for elderly. For class B drugs there is little research evidence, use experience or efficacy among persons aged 75 or older. Class C drugs are suitable for use in the elderly with caution and class D drugs should be avoided in the elderly.

4.2 Implicit Criteria to Indicate Inappropriate Prescribing

The Lipton criteria were developed and validated in the US in 1990 by using expert panel discussions and patient cases with the aim to implicitly measure appropriateness of prescribing (Lipton et al. 1992, Lipton et al. 1993). The tools is used to evaluate the appropriateness of each drug in the patient's regimen according to six categories; drug allergy, dosage, schedule, appropriateness of drug therapy choice (i.e., prescribed without an established diagnoses or being a less-than-optimal choice given the patient's overall health status), DDIs, and therapeutic duplication. Each category is scored by selecting one value (0=no problem, 1=potential problem, 2=definite problem, 9=not enough information to make a decision) for each drug, and the scores are summed to form a total prescribing score. Because the Lipton criteria were developed to measure prevalence of the drug-therapy problems, that had not been studied rigorously before, it lacks important dimensions of inappropriateness, like insufficient effectiveness and untreated conditions.

The Medication Appropriateness Index (MAI-index) was developed in the US in 1992 by using literature review and expert opinions (Hanlon et al. 1992). The MAI index measures the inappropriateness of prescribing by evaluating each drug used by ten criteria: indication**,** effectiveness, dosage, correct directions, DDIs, drug-disease interactions, practical directions, costs, duplication, and duration. Each medication is ranked as "appropriate", "marginally appropriate" or "inappropriate" according to these 10 dimensions (Hanlon et al. 1992). Later, weighted values from 1 to 3 were determined for each of the ten criterion (Samsa et al. 1994). By using the weightings, a single summated MAI score from 1 to 18 can be created for each medication used (Samsa et al. 1994). Three MAI domains related to unnecessary prescribing (lack of indication, lack of effectiveness, and therapeutic duplication) have been renamed "Unnecessary Drug Use Measure" (Suhrie et al. 2009).

Even though the MAI is more comprehensive than the Lipton criteria, it does not address underprescribing. As a result, an Assessment of Underutilization (AOU) tool was developed to supplement it (Jeffery et al. 1999). Using the tool a health care professional compares the patient's list of chronic conditions to the prescribed drugs and each condition is rated with "A=no omission", "B=marginal omission" or "C=omission".

4.3 Combination of Explicit and Implicit Criteria

Australian researchers have created their own set of prescribing indicators for elderly patients (aged >65 years) unrelated to any earlier prescribing criteria (Basger et al. 2008). The criteria are based on medications prescribed most frequently to Australians in 2006 and on the most frequent medical conditions for which elderly Australians consult a medical practitioner (Basger et al. 2008). The tool consists of 48 prescribing indicators, of which 45 are explicit and 3 implicit. Of the indicators 18 concern medications that should be avoided and 19 recommended medications in

certain diseases or conditions, 4 disease monitoring, 3 specific DDIs, 1 presence of any DDI, 1 vaccination status, 1 smoking and 1 addresses changes in medications in last 90 days. The tool is envisaged to form an important part of medication review process.

The quality indicators for drug use in elderly persons developed by the Swedish National Board of Health and Welfare (Socialstyrelsen 2003, 2010) can also be considered as a combination of explicit and implicit criteria. The Swedish indicators are based on international literature and currently include 9 drug-specific and 11 disease-specific indicators. The drug-specific criteria relate to: 1) Drugs that should be avoided e.g., long-acting benzodiazepines, drugs with a significant anticholinergic effect; 2) Drugs that necessitate a correct and timely indication, e.g., opioids, neuroleptics; 3) Inappropriate drug regimen: e.g., sedatives every night for more than a month, bowel-stimulating laxatives daily for more than a week; 4) Inappropriate dosing e.g., for some neuroleptics; 5) Inappropriate polypharmacy; e.g., use of two or more drugs from the same therapeutic group regularly, use of three or more psychotropic drugs; 6) Drug combinations that can lead to clinically significant interactions (i.e., class D according to FASS); 7) Drugs for which the use or dosing need to be adjusted according to kidney function, 8) Drugs that may cause or impair orthostatism, increase the risk for falls or impair cognition; and 9) Preferred and avoidable hypnotics and sedatives (Socialstyrelsen 2003, 2010). Disease specific indicators describe inappropriate and appropriate drug use in eleven common diseases in elderly persons, e.g., hypertonia, heart failure, pain and depression (Socialstyrelsen 2003, 2010).

4.4 Tools to Assess the Appropriateness of Elderly Patients' Pharmacotherapy in Finland

In Finland the first effort to guide appropriate prescribing and monitoring among the aged was developed by the National Institute of Medicines and Social Insurance Institution in 2007 when they published a booklet "Geriatric Pharmacotherapy" (Kivelä ja Räihä 2007). General section of the booklet describes specific features of geriatric pharmacotherapy, including ADRs and DDIs. Diagnoses-specific chapters focus on recommended treatments, including preferable and risky drug choices (Kivelä and Räihä 2007).

Of computerized programs to assess DDIs the one with the widest access in Finland by all healthcare professionals, including community pharmacists is the Swedish, Finnish, Interaction X-referencing database (SFINX) which in 2011 includes more than 12 000 DDIs (Böttinger et al. 2009, Lääkeinteraktiot SFINX). The SFINX is maintained by Finnish Medbase Oy, Swedish Karolinska Institutet and Stockholm county council, and updated four times a year by specialists of clinical pharmacology and pharmacotherapy. In SFINX interactions are classified according to their clinical significance from A to D, and according to the level of documentation from 0 to 4. Level D interactions are clinically significant and such combinations

should be avoided. Another readily available drug-interaction database is Drug-Reax® by Thomson Reuters (www.micromedex.com). In Drug-Reax® interactions are listed according to their severity (unknown, minor, moderate, major, contraindicated) and level of documentation (unknown, fair, good, excellent).

In order to assess the need to change the drug or alter drug doses due to impaired kidney function, the Renbase database can be used (Renbase 2011). The database is maintained by Medbase Oy and continuously updated by specialists in pharmacotherapy. The database covers all drug products licensed in Finland and includes information on more than 1000 instances of dosing and safety of drugs in different levels of kidney failure by taking into account different drug formulations. In the Renbase drugs are classified from A to D according to the need to avoid the drug or alter the drug dose. In class A no alterations are needed, in class B information is missing or is based on pharmacokinetic properties, in C there is need to alter drug dosage or dosing interval, and in D use of drug should be avoided.

4.5 Prevalence of Use of Potentially Inappropriate Medications (PIMs)

The prevalence of PIM use in different populations and settings has been widely studied (Aparasu and Mort 2000, Liu and Christensen 2002, Gallagher et al. 2007). The results are highly affected by the criteria that have been used (Fialova et al. 2005, van der Hooft et al. 2005, Barry et al. 2006, Bongue et al. 2009, Buck et al. 2009, Ryan et al. 2009a, Akazawa et al. 2010). The literature review for this thesis will solely focus on studies utilizing the Beers 2003 criteria (Fick et al. 2003).

4.5.1 PIM Use in the United States

In the US most PIM studies have been conducted by using the Beers 2003 criteria independent of diagnoses and conditions (Table 13). The corresponding prevalence of PIM use has in most studies been near 25%, but varied substantially from 15% to 53.5% (Table 13). The lowest prevalence was observed in demented patients of a National Alzheimer's Coordination Centre (Lau et al. 2010). The study with the highest prevalence described PIM use over a 3-year-period and is thus not comparable with other studies (Albert et al. 2010). The studies that have used the complete Beers 2003 criteria have involved small study populations and described prevalences ranging from 34% to 48.7% (Table 13). Overall, the studies with highest prevalences seem to be the ones that have used data from the first years of the 21st century (Zuckerman et al. 2006, Fick et al. 2008; Table 13). Because the populations and methods of data collection have differed, no conclusions of reduced PIM prescribing can be drawn from this finding. However, studies that have utilized Medical Expenditure Panel survey data, a nationally representative sample of community-

dwelling people aged ≥65 years, indicate reduction of PIM use between years 2001 (27.8%), 2005 (20.0%) and 2006 (16.0%) (Fu et al. 2007, Fu et al. 2010).

The most commonly used PIMs in the US studies have been largely the same (Table 13). Propoxyphene has been among the most prevalent PIMs in majority of studies. Also amitriptyline, anticholinergics and antihistamines, benzodiazepines, oral estrogens, fluoxetine, doxazosin and digoxin are mentioned frequently (Table 13).

4.5.2 PIM Use in Europe

The Beers 2003 criteria have been used in numerous European studies (Table 14). Fialova et al. (2005) studied the prevalence of PIM use among home care patients in 8 European countries: Denmark, the Netherlands, UK, Iceland, Norway, Finland, Italy, and Czech Republic. The prevalences according to the Beers 2003 independent of diagnoses varied from 5.8% in Denmark to 25.2% in Czech Republic and 25.7% in Italy (Fialova et al. 2005). In Finland, the prevalence of PM prescribing was 20.3%. The differences can be partly explained by different availability of Beers drugs in the studied countries, being highest in Italy. In other studies from individual European countries the prevalence of diagnoses-independent Beers 2003 PIM use has ranged from 11.6% in Ireland to 38.5% in Portugal (Table 14).

When diagnoses-dependent criteria are included, the prevalence of PIM use has varied between 13.0% in Ireland (Ryan et al. 2009a) and 33.6% in the UK (Table 14). Changes in PIM prescribing over the years have not been extensively studied in Europe. In the Netherlands van der Hooft et al. (2005) found no difference in PIM prescribing between 1997–2001. In the UK PIM use remained stable between 1994–2003 (De Wilde et al. 2007), but decreased between 1996–2005 after commonly used propoxyphene was removed from the market (Carey et al. 2008).

More consistently than in the US studies, benzodiazepines have been involved as one of the most prevalent PIMs in all European studies (Table 14). The exceptions to this are two Italian studies, in which benzodiazepines were excluded from the analysis (Maio et al. 2006b, Maio et al. 2010). Other common PIMs in European studies have been, e.g., amitriptyline, ticlodipine and amiodarone (Table 14).

4.5.3 PIM Use Outside the United States and Europe

In countries outside the US and Europe, the prevalence of PIM prescribing in Australia resembles the situation in Europe both regarding the prevalence and commonly used PIMs (Table 15). Also in other countries the prevalences resemble European results, but involved small patient populations (Saab et al. 2006, Zaveri et al. 2010, Lin et al. 2011) which may impair the reliability of the results. For example, in a large Taiwanese study with more than 176 million outpatient visits the annual prevalence of PIM use, independent of diagnoses, was over 60% while in smaller cross-sectional studies it varied from 23.7% to 27.5% (Table 15).

4.5.4 Factors Associated with PIM Use

Use of PIMs has been consistently associated with female gender and higher number of medications used (Tables 13–15). In addition, higher number of chronic diseases has predicted PIM use in several studies (Tables 13–15). Other factors associated with PIM use are, for example, history of depression (Blalock et al. 2005, Akazawa et al. 2010, Weston et al. 2010) and poor economic situation (Fialova et al. 2005, Maio et al. 2006b). In some studies older age has been a protective factor (Fialova et al. 2005, Barnett et al. 2011), in others a risk for PIM use (Maio et al. 2006b, Landi et al. 2007a, Carey et al. 2008, Lin et al. 2008, Maio et al. 2010, Lin et al. 2011).

Table 13. *Potentially inappropriate medication (PIM) use according to the Beers 2003 criteria (Fick et al. 2003) in the community setting in the United States. Presented in alphabetical order.*

Article	Criteria	Population (n), age	Data source, year	Prevalence (%)	Most common PIMs	PIM use associated with
Albert et al. 2010	Beers 2003 iDg	Retirees from a single large corporation aged ≥65 years (n=7 459)	Employer prescription claims, 2003–2005	53.5% over 3 years	Diazepam, amitriptyline, (dextro)propoxyphene, short-acting nifedipine, doxazosin	
Blalock et al. 2005	Beers 2003 iDg, estrogens excluded	Rural community-dwelling elderly aged ≥65 years (n=800)	Face-to-face interviews at home between 2002–2004	26.6 %	Propoxyphene, clonidine, naproxen, amiodarone	Lower social support, poorer health status, higher disability, higher number of medications, history of major depression
Buck et al. 2009	Beers 2003 iDg, estrogens excluded	Patients with at least 2 primary care visits in the previous 2 years, aged ≥65 (n=61 251)	Practice electronic health records, Apr 2006	Utah: 23.3% Ohio: 23.0%	Propoxyphene, fluoxetine, amitriptyline, doxazosin	Female sex, polypharmacy (≥6 medications), number of primary care visits
Fick et al. 2008	Beers 2003 iDg	Medicare managed care patients aged ≥65 years (n=16 877)	Administrative database claims data, Jan–Jun 2000	40.7%	Estrogens only, propoxyphene, short-acting benzodiazepines, digoxin, longer half-life NSAIDs	
Fu et al. 2007	Beers 2003 iDg	Nationally representative sample of non-institutionalized aged ≥65 (n=1 161)	Medical Expenditure Panel Survey data from 2001	27.8% in 2001	Propoxyphene, digoxin > 0.125 mg, amitriptyline	Higher mean number of prescriptions
Fu et al. 2010	Beers 2003 iDg	Nationally representative community-dwelling sample, aged ≥65 years (n=1 774)	Medical Expenditure Panel Survey data in 2005 and in 2006	20.0% in 2005 16.0% in 2006	Anticholinergics and antihistamines, propoxyphene, digoxin	Enrollment in Medicare part D

Article	Criteria	Population (n), age	Data source	Prevalence	Most common PIMs	PIM use associated with
Golden et al. 2011	Beers 2003 iDg with severity rating 'high'	Homebound adults eligible for Medicare and Medicaid, aged ≥65 years (n=3 911)	Home assessment in late 2009	25.2%	Diphenhydramine, high-dose short-acting benzodiazepines, oxybutynin, fluoxetine, promethazine, hydroxyzine	
Lau et al. 2010	Beers 2003 iDg, iDo	Community-dwelling patients with (n=1 853) and without dementia (n=2 665) aged ≥65 years	National Alzheimer's Coordinating Centre Uniform Data Set from initial visits Sep 2005–Sep 2007	20% of patients without dementia, 15% with dementia	Oral estrogens, muscle relaxants/antispasmodics, fluoxetine, short-acting nifedipine, doxazosin	Higher number of medications, female gender
Lund et al. 2010	Beers 2003 (all)	Veterans aged ≥65 visiting primary care clinics (n=236)	Interview and medical record review at study enrolment	48.7%	NS	
Maio et al. 2006a	Beers 2003 iDg	Patients of 2 outpatient practices aged ≥65 years (n=100)	Chart review Jan–June 2004	24%	Fluoxetine, oral estrogens, diazepam, indomethacin, naproxen, dicyclomine	Female gender, not being a high school graduate, higher number of medications and diagnoses
Roth and Ivey 2005	Beers 2003 (all)	Community-dwelling aged ≥60 (n=100)	Home-visit May–July 2002	34%	NS	
Steinman et al. 2006	Beers 2003 (all)	Outpatient veterans using 5 or more medications, aged ≥65 years (n=196)	In-person interview and chart review at veterans clinic 2001–2003	37%	Digoxin, amitriptyline, oxybutynin	Increasing number of drugs
Zuckerman et al. 2006	Beers 2003 iDg, iDo, iDu	Convenience sample of privately insured patients aged ≥65 (n=487 383)	Drug benefit database, year 2000	41.9%	Hormones (systemic estrogen and methyltestosterone), analgesics (propoxyphene, meperidine, pentazocine)	
iDg=independent of diagnoses, iDo=independent of dosage, iDu=independent of duration of treatment						

Table 14. *Potentially inappropriate medication (PIM) use according to the Beers 2003 criteria (Fick et al. 2003) in the community setting in Europe. Presented in alphabetical order.*

Article, country	Criteria	Population (n), age	Data source, year	Prevalence (%)	Most common PIMs	PIM use associated with
Barnett et al. 2011 Scotland	Beers 2003 iDg	Community-dwelling residents aged 66–99 years (n=65 742)	Health care data in 2005–2006 (2 years)	30.9%	Amitriptyline, ferrous sulphate, long-acting benzodiazepines	Female gender, younger age, higher polypharmacy, living in nursing or residential home
Berdot et al. 2009 France	Beers 2003 iDg, iDo	Non-institutionalized patients from 3 cities, aged ≥65 (n=6 343)	Face-to-face interview 1999–2000	31.6%	Cerebral vasodilators, long-acting benzodiazepines, short-acting benzodiazepines	
Carey et al. 2008 UK	Modified Beers 2003 (all)[a]	Primary care patients aged ≥65 years (n=approximately 230 000/year)	Primary care database from 201 practices, years 1996–2005	1996: 32.2% 2005: 28.3%	NS	Number of drugs (strong association), female gender, older age, living in a care home
Fialova et al. 2005 8 European countries[b]	Beers 2003 iDg, iDu	Home care patients aged ≥65 years from country's urban area (n=2 707) (n=187–428/country)	Patient interview, medical records Sep 2001–Jan 2002	16.9%, 5.8–25.7% / country Finland: 20.3%	Diazepam, amiodarone, amitriptyline, ticlodipine In Finland: diazepam, amitriptyline, short-acting nifedipine	Poor economic situation, users of anxiolytic drugs, use of >6 medications. Less likely: aged ≥85 years, living alone
Fiss et al. 2011 Germany	Beers 2003 iDg	HMR patients aged ≥65 years (n=744)	In-home interviews Mar 2006–Dec 2008	18%	Benzodiazepines, amitriptyline, doxepin	
van der Hooft et al. 2005 The Netherlands	Beers 2003 (cDg, iDu)	Ambulatory older people aged ≥65 years (n=18 030–26 378/ study year)	Computer-based patient records of 150 GPs, years1997–2001	19.1–20%	Nitrofurantoin, diazepam, amitriptyline, temazepam >15mg	
Landi et al. 2007a Italy	Beers 2003 iDg	Community-living patients aged ≥80 from Central Italy (n=364)	In-home interviews Dec 2003–Sep 2004	26.0%	Long-acting and short-acting benzodiazepines, short-acting nifedipine, ticlopidine	Older age, cognitive impairment, higher number of medications

Article, country	Criteria	Population (n), age	Data source, year	Prevalence (%)	Most common PIMs	PIM use associated with
Maio et al. 2006b Italy	Italian Beers 2003[c] (iDg, iDo, iDu)	Outpatients aged ≥65 with ≥1 prescription in 2001 living in one Northern Italian region (n=849 425)	Outpatient prescription claims database, year 2001	17.9%	Doxazosin, ketorolac, ticlopidine, amiodarone	Older age, number of chronic disease and medications, male sex, low income
Maio et al. 2010 Italy	like Mayo et al. 2006b	Outpatients aged ≥65 with ≥1 prescription in 2006 (n=91 741)	Local outpatient prescription data-base, year 2006	25.8%	NSAIDs, ticlodipine, doxazosin, amiodarone	Older age, higher number of chronic diseases and medications, female gender
De Oliveira Martins et al. 2006 Portugal	Beers 2003 iDg	Outpatients presenting a prescription in of 12 community pharmacies, aged ≥65 (n=213)	Patient interview Oct 2002–Jan 2003	38.5%	Diazepam, ticlopidine, amiodarone	
Ryan et al. 2009a Ireland	Beers 2003 (all)	Primary care patients alphabetically selected from surgery's database, aged ≥65 years (n=500)	Surgery's paper-based and electronic medical records May–Oct 2006	13.0% (11.6% iDg)	Doxazosin, diazepam, ferrous sulphate >325 mg cDg: depression and long-term benzodiazepine	
Ryan et al. 2009b Ireland	Beers 2003 (all)	Primary care patients aged ≥65 years (n=1 329)	Case records from 3 general practices Jan 2007–Jul 2008	18.3%	Doxazosin, diazepam, flurazepam cDg: depression and long-term benzodiazepine	
DeWilde et al. 2007 UK	Beers 2003 (all)	Primary care patients (includes nursing home patients) aged ≥65 years (annual n=130 262–177 123)	Primary care database of 131 practices 1994–2003	Beers iDg 28.9–31.2% Beers all 32.2–33.6%	Dextropropoxyphene, amitriptyline, long-acting benzodiazepines, doxazosin, ferrous sulphate >325 mg/day	

cGg=cum diagnoses, iDg=independent of diagnoses, iDo=independent of dosage, iDu=independent of duration of treatment
[a] additional benzodiazepines, amitriptyline only >50 mg, [b] Denmark, Italy, Iceland, Norway, Finland, UK, the Netherlands, Czech Republic, [c] only reimbursable drugs

Table 15. *Potentially inappropriate medication (PIM) use according to the Beers 2003 criteria (Fick et al. 2003) in the community setting in countries outside the US and Europe. Presented in alphabetical order.*

Article, country	Criteria	Population (n), age	Data source, year	Prevalence (%)	Most common PIMs	PIM use associated with
Akazawa et al. 2010 Japan	Beers 2003 iDg	Patients with at least 2 pharmacy claims over 1-year period, aged ≥65 years (n=6 628)	Health insurance claims data Apr 2006–Mar 2007	28.5%	Benzodiazepines, anticholinergics and antihistamines	Polypharmacy, inpatient service use, comorbidities of peptic ulcer, depression or cardiac arrhythmias
Castelino et al. 2010b Australia	Beers 2003 cDg	Community-dwelling elderly receiving HMR, aged ≥65 years (n=372)	HMR case reports, year NS	39.8%	Diazepam, amiodarone, amitriptyline, propoxyphene	
Lai et al. 2009 Taiwan	Beers 2003 with high severity, iDo, iDg	Ambulatory care visits (n=176 661 994) involving a prescription by patients aged ≥65 years	National Health Insurance claims database in 2001–2004	62.5% of patients in 2004, 65.7% in 2001	Anticholinergic antihistamines, muscle relaxants/antispasmodics, long-acting benzodiazepines	Female gender, number of drugs prescribed during a visit
Lin et al. 2008 Taiwan	Beers 2003 iDg	Ambulatory patients aged ≥65 years prescribed long-term medications from a tertiary medical centre (n=5 741)	Claims data to bureau of National Health Insurance, Mar 2005	23.7%	Dipyridamole, doxazosin, amiodarone, chlorzoxazone	Female sex, older age, higher number of chronic diseases and medications
Lin et al. 2011 Taiwan	Beers 2003 iDg	Community-dwelling patients visiting an outpatient clinic, aged ≥65 years (n=327)	Recorded at clinic, Aug 2008	27.5%	Orphenadrine, chlorpheniramine, cyproheptadine	Older age, higher number of prescribed drugs, diagnoses of acute diseases

Article, country	Criteria	Population (n), age	Data source, year	Prevalence (%)	Most common PIMs	PIM use associated with
Roughead et al. 2007 Australia	Combined Beers 2003 and McLeod iDg, iDo, (only reimbursable drugs)	Veterans with eligible gold card aged ≥70 years (n=192 363)	Repatriation Pharmaceutical Benefits Scheme Pharmacy Claims database Jan–June 2005 (6 months)	21.2%	Long-acting benzodiazepines, amitriptyline, amiodarone	
Saab et al. 2006 Lebanon	Beers 2003 iDg	Patients of 10 community pharmacies aged ≥65 years (n=277)	Pharmacy records and in-person interviews Nov 2004–May 2005	22.4%	Propoxyphene, dipyridamole, doxepin, meprobamate	(Data stated only for wider range of inappropriate prescribing i.e., combination of PIMs, missing doses, DDI, duplication etc.)
Zaveri et al. 2010 India	Beers 2003 (all)	Patients presented to outpatient department of tertiary hospital, aged ≥65 (n=407)	Data source not stated Nov 2005–Feb 2006	23.6%	Pheniramine, digoxin, chlorpheniramine, phenylpropanolamine with hypertension	
cDg=cum diagnoses, iDg=independent of diagnoses, iDo=independent of dosage, iDu=independent of duration of treatment						

4.6 Negative Outcomes and Risks Associated with the Use of Potentially Inappropriate Medications

Evidence on the risks of PIM use is controversial and inconclusive (Jano and Aparasu 2007; Table 16). Jano and Aparasu (2007) reviewed the literature from October 1991 to October 2006 to examine health outcomes associated with PIM use according to the Beers criteria (Beers et al. 1991, Beers 1997, Fick et al. 2003) among elderly patients in different health care settings. This literature review will complement the Jano and Aparasu (2007) review with more recent studies (Table 16) but in line with other parts of this thesis will focus only on studies on community-dwelling people and applying the Beers 2003 criteria (Fick et al. 2003).

Based on the review by Jano and Aparasu (2007), the use of PIMs was associated with hospitalization among community-dwelling elderly. Since the review was published several new articles have appeared (Table 16) and have confirmed the association (Fick et al. 2008, Lin et al. 2008, Lai et al. 2009, Akazawa et al. 2010, Albert et al. 2010). In Ireland a prospective observational study indicated that 16% of 597 consecutive acute hospital admissions could be linked to adverse effects of Beers 2003 PIMs (Gallagher et al. 2008b). Of the patients receiving PIMs (n=191), 49% had conditions that were likely to be adverse effects of PIMs, for example falls, gastrointestinal bleed or cognitive deterioration. However, in another Irish study (Gallagher and O'Mahony 2008) Beers criteria PIMs were contributory or causal only in 6% of acute admissions to hospital by elderly patients. In the same study, STOPP-criteria identified a significantly higher proportion of patients requiring hospitalization as a result of PIM-related ADE than the Beers criteria (11.5% vs. 6%).

No association between PIM use and health care use other than hospitalizations or mortality was found among community-dwelling people in the review by Jano and Aparasu (2007). With regard to mortality, more recent studies have provided similar results (Table 16; Lin et al. 2008, Barnett et al. 2011). However, several recent studies have found an association between PIM use and higher health care utilization, for example higher number of outpatient or ambulatory care visits (Fick et al. 2008, Lai et al. 2009, Akazawa et al. 2010) and emergency department (ED) visits (Fick et al. 2008, Lai et al. 2009). For ED visits the association is not indisputable and other drugs than PIMs may play a greater role (Budnitz et al. 2007, Lin et al. 2008). At least in an US survey only 3.6% of outpatient ED visits due to an ADE among patients aged ≥65 years were caused by diagnoses-independent PIMs and additional 5.2% by diagnoses-dependent PIMs (Budnitz et al. 2007). In comparison, the percentage was 17.3% for warfarin, 13.0% for insulin and 3.2% for digoxin. Accounting for outpatient prescription frequency, the risk for ED visits for these 3 medications was 35 times greater than for diagnoses-independent PIMs.

Interestingly, in a large US cohort study (n=487 383) the use of PIMs increased the risk of nursing home admission by 31% but PIM hormones were found to have a protective effect (Zuckerman et al. 2006). On the other hand, antipsychotics, antiemetics and analgesics had higher relative risks ranging from 1.97 to 2.03. The authors concluded, that the risks associated with nursing home admissions may be

explained by the underlying conditions rather than the PIM use. Also, it can be possible that some PIMs pose more risks than the others.

There are some studies that indicate PIMs to be associated with ADEs and ADRs (Jano and Aparasu 2007, Table 16). However, in several recent studies in the community setting no association between PIM use and self-reported ADEs has been found (Table 16; Lund et al. 2010, Shiyanbola and Harris 2010, Fiss et al. 2011). Similar to ED visits, it is possible that PIMs are not the most significant drug group causing ADRs (Laroche et al. 2007b). In a French study among outpatients aged ≥70 years admitted to hospital the ADR prevalence was higher among PIM users according to the French modification of Beers criteria than among non-users (20.4% vs. 16.4%) but after adjustment for confounding factors the difference was not statistically significant (Laroche et al. 2007b). In addition, among PIM users only 5.9% of ADRs were directly related to PIMs. Instead, majority of drugs involved in ADRs (47.5%) were diuretics and other cardiovascular drugs.

Falls, a common ADR in elderly patients, may be more common among PIM users (Agashivala and Wu 2009, Berdot et al. 2009, Fiss et al. 2011). In a French study, the association was mainly due to long-acting benzodiazepines and other psychotropics and anticholinergic medications (Berdot et al. 2009). No association was found for short- or intermediate-acting benzodiazepines either in occasional or regular use. When risk for fractures is considered, there has been no difference between users of Beers-criteria benzodiazepines or users of other benzodiazepines (van der Hooft et al. 2008b). Instead, the risk for fractures was greater for high doses (>10 mg diazepam dose equivalents) or longer-duration treatments (14–90 days), irrespective of the half-life of the benzodiazepine (van der Hooft et al. 2008b). On the other hand, in nursing home setting the risk for falls for non-Beers 2003 psychoactive drugs was smaller (OR 0.83, p=0.028) than for those psychoactive drugs listed in the Beers 2003 criteria (Agashivala and Wu 2009).

Some studies have been published with regard to the effects of PIM use on HRQoL (Jano and Aparasu 2007, Landi et al. 2007a). Again, the results are highly inconsistent. Still, poorer HRQoL, worse self-perceived health status and impairment of physical performance have been reported (Chin et al. 1999, Fu et al. 2004, Landi et al. 2007a).

According to the review by Jano and Aparasu (2007), the use of PIMs was associated with increased costs in all health care settings. Later Fu et al. (2007) estimated the incremental health care expenditures (related to both drug costs and health care visits and stays) due to Beers 2003 PIM use in the community-dwelling elderly in the US to be USD 7.2 billion in 2001. In Japan, the use of PIMs was associated with 33% higher total medical cost after adjusting for confounding factors (Akazawa et al. 2010).

In conclusion, the results on the adverse outcomes associated with PIM use among community-dwelling elderly remain controversial and inconclusive, but suggest that actions to reduce PIM prescribing and use are reasonable.

Table 16. *Adverse health outcomes associated with potentially inappropriate medication (PIM) use according to the Beers 2003 criteria (Fick et al. 2003) in the community setting, excluding studies reviewer earlier (Jano and Aparasu 2007). Presented in alphabetical order.*

Study	Criteria	Study design	Population (n)	Effect on outcome	No effect on outcome
Akazawa et al. 2010	Japanese Beers 2003	Retrospective cohort (1 year)	Outpatients with at least 2 pharmacy claims, aged ≥65 years (n=6 628)	Outpatient days (Incidence rate ratio1.18), hospitalization (OR 1.68), health expenses (33% increased, including medical and pharmacy services), each p<0.001	
Albert et al. 2010	Beers 2003	Retrospective cohort (3 years)	Retirees (n=7 459), 96% aged ≥65 years	Hospitalization (OR 1.78)	
Barnett et al. 2011	Beers 2003 iDg	Retrospective cohort (2 years)	Community-dwelling (n=65 742) and in care patients (n=4 557), aged ≥65 years		Mortality (OR 0.98)
Berdot et al. 2009	Combined Beers 1997, 2003 and French criteria iDo, iDu, iDg	Multicentre prospective cohort (4 years)	Non-institutionalized aged ≥65 years (n=6 343)	Falls (if cerebral vasodilators excluded, both occasional (OR 1.22, p=0.03) and regular (OR 1.19, p=0.049) PIM use, if cerebral vasodilators included, only occasional use (OR 1.23, p=0.016))	
Fick et al. 2008	Beers 2003 iDg	Retrospective cohort (6 months)	Community-dwelling aged ≥65 years (n=16 877)	Higher prevalence of DRPs i.e., ADEs (14.5% vs. 4.7%; p<0.01), inpatient visits (OR 1.99), outpatient visits (OR 1.53), office visits (OR 1.89), ED visits (OR 1.98) and higher healthcare costs (p<0.01)	
Fiss et al. 2011	Beers 2003 (all)	Prospective cohort	HMR patients aged ≥65 years (n=744)	Slight association with self-reported falls (φ coefficient 0.1074, p=0.024)	Self-reported ADR (φ coefficient 0.0185, p=0.619)
Fu et al. 2007	Beers 2003 iDg	Retrospective cohort (1 year)	Community-dwelling, aged ≥65 years (n=720)	Higher health care expenditures compared to nonusers (p<0.05)	
Lai et al. 2009	Beers 2003 iDg, iDo, high risk PIMs	Retrospective, cross-sectional	Patients with ambulatory care visits, aged ≥65 years (n=2 133 864 in 2004)	Higher mean number of ambulatory care visits (30.78 vs. 16.57; p<0.001), ED visits (0.27 vs. 0.15, p<0.001) and hospital admissions (0.46 vs. 0.27, p<0.001)	

Study	Criteria	Study design	Population (n)	Effect on outcome	No effect on outcome
Landi et al. 2007a	Beers 2003 iDg	Cross-sectional	Community-dwelling, aged ≥80 years (n=364)	Impaired physical performance compared to non-users (Short Physical Performance Battery Score 7.04 vs. 6.16; p=0.01). If ≥ 2 PIMs: poorer functional status (ADL scale score) compared to nonusers (p=0.01) and users of 1 PIM (p=0.03)	Muscle strength
Lin et al. 2008	Beers 2003 iDg	Prospective cohort (6 months)	Ambulatory, aged ≥65 years (n=5 741)	Hospitalization (OR 1.62; p=0.03)	Death (OR 1.71, p=0.567), ED visits (OR 1.13, p=0.481)
Lund et al. 2010	Beers 2003 (all)	Prospective cohort (3 months)	Community-dwelling veterans aged ≥65 years (n=236)		Self-reported ADE (OR 1.43, p=0.39)
Shiyanbola and Farris 2010	Combination of Beers 2003 and ACOVE quality indicators	Cross-sectional survey	Outpatients (Medicare beneficiaries) aged ≥65 years (n=874)		Self-reported ADE

ADE=Adverse drug effect, ADL=Activities in daily living, ADR=Adverse drug reaction, iDg= independent of diagnoses, iDo=independent of dose, iDu=independent of duration of treatment, ED=Emergency department, OR=Odds ratio

5 Aims of the Study

This study consists of 4 substudies (Table 17) which examine the Finnish Comprehensive Medication Review (CMR) model as a means to improve the appropriateness and safety of pharmacotherapy among community-dwelling patients aged ≥65 years. The specific aims of the study were:

1) To determine the prevalence of potentially inappropriate medication use according to the Beers 2003 criteria among Finnish non-institutionalized population aged ≥65 years, and the reimbursement costs for these medications (I)
2) To describe the development of the CMR accreditation training and the curriculum used in it. To assess the participants' perceptions about the training (II)
3) To describe the development and contents of the CMR model. To develop documentation forms for CMR and assess CMR training participants' satisfaction on the documentation (III)
4) To evaluate the DRPs detected and reported to physicians during CMR. To identify drugs most commonly involved in the DRPs and the interventions resulting from the CMRs among outpatients aged ≥65 years (IV)

Table 17. *Methods used in the substudies (I-IV)*

STUDY	METHODS	POPULATIONS	ANALYSIS
I	Analysis of PIM use and costs obtained from the national reimbursement data	National non-institutionalized population aged ≥65 years in 2007 (n=841 509)	Quantitative analysis; descriptive statistics (frequencies, percentages)
II	Description of the development of CMR training, Internet survey in 2008	CMR accreditation training participants attending courses in Helsinki and Oulu (n=38), response rate 90%	Quantitative analysis; descriptive statistics (frequencies, percentages, means, standard deviations), qualitative content analysis of open-ended questions
III	Description of the development of CMR procedure and related literature review, survey in 2008	CMR accreditation training participants attending courses in Helsinki and Oulu, responses of community pharmacists (n=27), response rate 84%	Quantitative analysis; descriptive statistics (frequencies, percentages), qualitative content analysis of open-ended questions
IV	Analysis of CMR case reports to evaluate drug-related problems identified by participants of CMR accreditation training	Home-dwelling (n=70) and assisted-living (n=51) CMR patients aged ≥65 years	Quantitative analysis; descriptive statistics (frequencies, percentages), statistical analyzes; t-test, Mann-Whitney U-test, Pearson Chi-Square test

6 Materials and Methods

6.1 Study Populations

6.1.1 National Outpatient Population Aged 65 and Older (I)

The cross-sectional register-based study involved the entire non-institutionalized population of Finland aged 65 or older in 2007. Since the analyzed Social Insurance Institution (SII) data included persons deceased during 2007, the number of total elderly population was retrieved from the national population statistics of December 31, 2006 (Statistics Finland 2010). Institutionalized care in Finland is the responsibility of municipalities, and the number of inpatients is based on municipal statistics as of December 31, 2006 (Sjöholm 2008). In 2007 there were in total 868 717 inhabitants aged ≥65 in Finland (Statistics Finland 2010). Of these 27 208 (3.1%) were living in institutionalized setting (Sjöholm 2008). Thus, the population in the substudy IV consisted of 841 509 non-institutionalized persons aged ≥65 years.

6.1.2 CMR Accreditation Training Participants (II, III, IV)

The three substudies related to the development of CMR procedure (II, III, IV) involved CMR accreditation training participants in 2005–2007 (Table 18). The pilot training participants (n=26) were involved in the development of the CMR accreditation training curriculum, the CMR procedure and the CMR documentation. The training participants were practicing community and hospital pharmacists from different parts of Finland. They were selected according to predetermined criteria, which required e.g., that the applicants had ongoing cooperation with local health care providers, particularly with physicians.

Of the 42 accreditation training participants in 2006–2007 in Helsinki and Oulu 38 responded to an internet-based survey regarding their perceptions of the CMR training (response rate 90.5%). The same training participants were also consulted using another survey to assess their satisfaction and ideas on improving the CMR documentation. This second survey was targeted only to community pharmacists (n=32), because the hospital pharmacists indicated that they rarely had the opportunity to use the entire CMR documentation in busy hospital settings. Responses were received from 27 community pharmacists (response rate 84.4%). However, of the 32 community pharmacists two did not use the documentation because they did not have any patients for CMR during the accreditation training period. Thus, the response rate among those having actually applied the documentation was 90.0%.

Table 18. *CMR accreditation training course participants involved in the substudies II-IV*

Course, year	Place	Participants (n)		Involvement in the substudies II–IV
		Community pharmacists	Hospital pharmacists	
Pilot 2005–2006	Kuopio[a]	21	5	Development of the CMR accreditation training curriculum (II) Development of the CMR procedure (III) Development of the CMR documentation (III)
2006–2007	Helsinki[a]	17	5	Testing of the CMR accreditation training curriculum (II) and providing their perceptions on the training (II) Testing of the CMR procedure and documentation (III) Providing development needs of the CMR documentation (III) Providing conducted CMR cases for the DRP analysis (IV)
	Oulu[a]	15	5[b]	

[a] All the training courses included practicing pharmacists from different parts of Finland
[b] One hospital pharmacist discontinued the accreditation training

6.1.3 Patients Receiving CMR (IV)

The 32 community pharmacist participating in the CMR accreditation training in Helsinki and Oulu in 2006–2007 were asked to submit anonymous case reports of the CMRs they conducted during the training for use in this study. The patients for CMR were selected by the collaborating physicians based on potential problems in their pharmacotherapy, e.g., suspected ADRs, poor adherence or excessive polypharmacy. An informed consent was requested from the patients or their authorized representatives both to participate in the CMR and to use the anonymous case reports in this study. The cases were included if written consent was received, if they were a primary care patient aged ≥65 years and if the documentation of the case conference was available. Of the total 166 CMRs conducted, 121 were included and 45 excluded (Figure 8). The 121 included case reports were received from 26 community pharmacists (Figure 8).

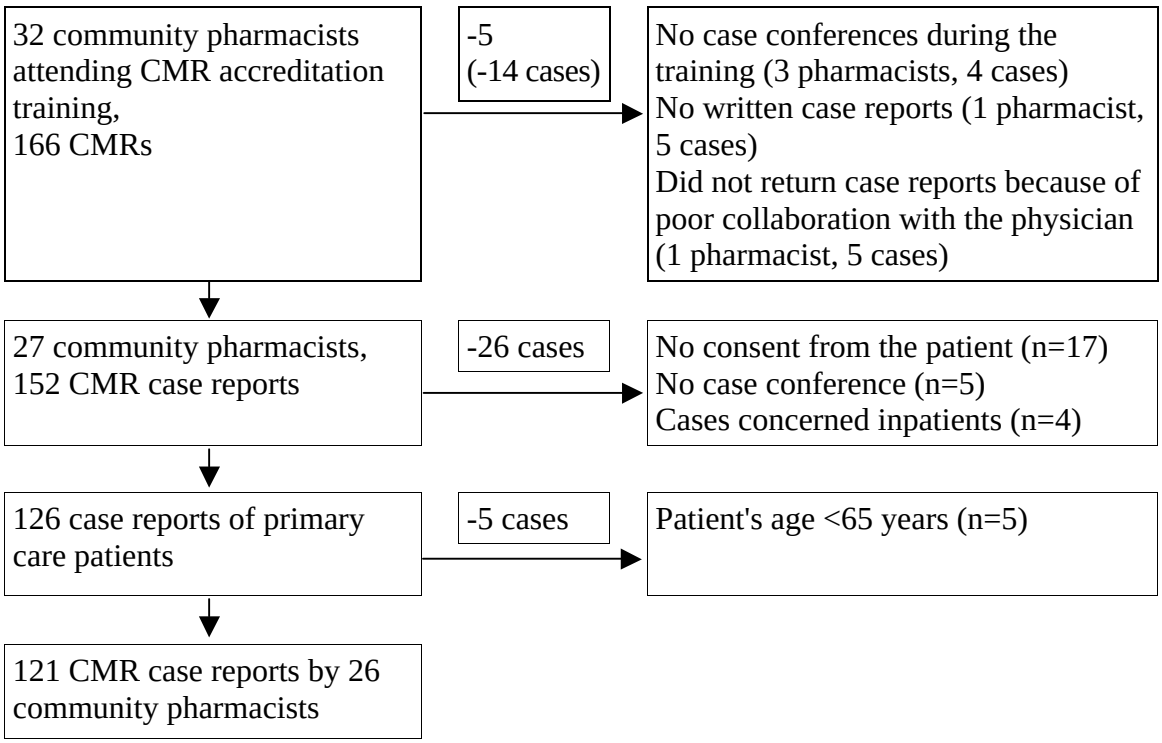

Figure 8 *Inclusion of CMRs by community pharmacists under accreditation training for the substudy IV*

Of the 121 CMR patients, 57.9% (n=70) were living in their own homes and 42.1% (n=51) in assisted living settings (Table 19). Mean age of the patients was 80.0 years, and mean number of regular prescription drugs 12.3. There was no difference in the age and mean number of used prescription drugs between home-dwelling and assisted-living patients (Table 19). However, the home-dwelling patients were using more 'as needed' prescription drugs and OTC drugs than the assisted-living patients (Table 19). Seventy-nine percent of the patients used regularly ≥10 prescription drugs.

Table 19. *Characteristics of CMR patients (n=121) according to the place of living*

Characteristic	**All (n=121)**	**Home (n=70)**	**Assisted-living (n=51)**	**p**
Gender				
Women, n (%)	87 (71.9)	53 (75.7)	34 (66.7)	
Age, mean (range)	80.0 (65–95)	79.6 (65–91)	80.5 (66–95)	NS[a]
Drugs, n mean (range)				
Regular prescription drugs	12.3 (4–23)	12.5 (4–22)	12.0 (6–23)	NS[b]
As needed prescription drugs	2.8 (0–9)	3.2 (0–9)	2.1 (0–9)	0.002[a]
Over-the-counter drugs	2.2 (0–11)	2.7 (0–10)	1.5 (0–11)	0.001[a]

[a] the Mann-Whitney *U* test, [b] independent sample *t*-test
NS=Not significant

6.2 Methods

6.2.1 Use of Potentially Inappropriate Medications (PIMs) Among Non-Institutionalized Population Aged 65 and Older (I)

The Social Insurance Institution (SII) maintains a national prescription register of all reimbursed drug purchases by outpatients in Finland. Drugs are approved for the reimbursement scheme by the Pharmaceutical Pricing Board under the Ministry of Social Affairs and Health, based on both clinical significance and the price of the product (Wahlbeck et al. 2008). As the scheme is planned to support mainly long-term therapies for chronic diseases, small package sizes of 10–30 tablets are usually not reimbursed, other than medicines such as antimicrobials used to treat some short-term conditions.

The data for this study consisted of extraction from the SII prescription register of all reimbursed drugs for outpatients aged ≥65 years in 2007. The drugs were classified on the fifth level of the Anatomical Therapeutic Chemical (ATC) classification system (WHO 2011). For each drug, the data includes the total number of individuals aged ≥65 years who had received reimbursements of that drug. The following data were derived from the obtained SII data: 1) PIMs, independent of diagnoses (Fick et al. 2003), including drug formulations that could only be administered orally; 2) the number of elderly outpatients who had received reimbursements for each PIM during 2007; and 3) the total reimbursements (€) paid for each PIM. For PIMs that were not identifiable based on the fifth level of ATC classification, additional data was acquired from the SII using Nordic article codes available for identifying each marketed drug product (Pharmaceutical Information Centre 2007). These product codes were used to separate long- and short-acting forms of oxybutynin, dipyridamole and nifedipine preparations. The same method was used to separate oral versus local estrogens; temazepam 10 mg and 20 mg tablets; and digoxin 0.0625 mg, 0.125 mg and 0.25 mg tablets. To determine the total number of PIM users in 2007, relevant ATC codes or Nordic article codes were linked to personal identity numbers in the SII.

The 2003 version of the Beers criteria (Fick et al. 2003), independent of diagnoses or conditions, was used to evaluate PIM use. These criteria were selected because they are a commonly used tool to address PIM use in international studies (Tables 13–15) and thus, allow the best comparison of results. Secondly, the criteria are suitable to be used in large population databases.

The Beers criteria were adopted by excluding the drugs not licensed in Finland in 2007. Of the 78 drugs listed in the original Beers 2003 criteria, 37 (47.4%) were marketed as oral preparations in Finland during the study period (Table 12). Drugs considered potentially inappropriate because of dosage or duration of treatment (lorazepam, oxazepam, alprazolam, naproxen and piroxicam) were excluded because the SII data do not contain this information. The only exceptions to this exclusion were digoxin and temazepam, which were available in strengths exceeding dose limits of the Beers criteria.

6.2.2 Development of the CMR Accreditation Training and Procedure (II, III)

The development of the CMR accreditation training and the CMR procedure started as a part of the TIPPA follow-up program in 2004 (TIPPA Project 2004, Figure 9). The TIPPA Coordination Group which included representatives from the key pharmacy stakeholders, i.e., universities, continuing education centers and professional organizations planned and coordinated this work. Aducate, Center for Training and Development, University of Eastern Finland, was responsible for organizing the CMR training.

Before starting the actual development of the CMR training and procedure, suitable models for them were sought from abroad (Hakkarainen 2008). No long-term trainings for CMR were found, and thus the curriculum was developed by the TIPPA Coordination Group. Australian Home Medicines Review (HMR; Sorensen et al. 2004) and US Medication Therapy Management (MTM; JAPhA and NACDS 2005) service models were found to be suitable as examples for the CMR procedure development. To develop and test the CMR curriculum and various CMR models a CMR pilot training was started in 2005. During the training, the participants were introduced to the principles of clinical medication reviews and procedures used in Australia and USA. Then they were asked to develop a CMR procedure/model in collaboration with physicians and other health care professionals to fit their local health care environment. These potential procedures were combined to form a national standard CMR procedure by the TIPPA Coordination Group. The Group also accepted the final CMR accreditation training model. Both the CMR accreditation training and the uniform CMR model were tested in practice by participants in two upcoming CMR trainings which were started in 2006 in Helsinki and in Oulu.

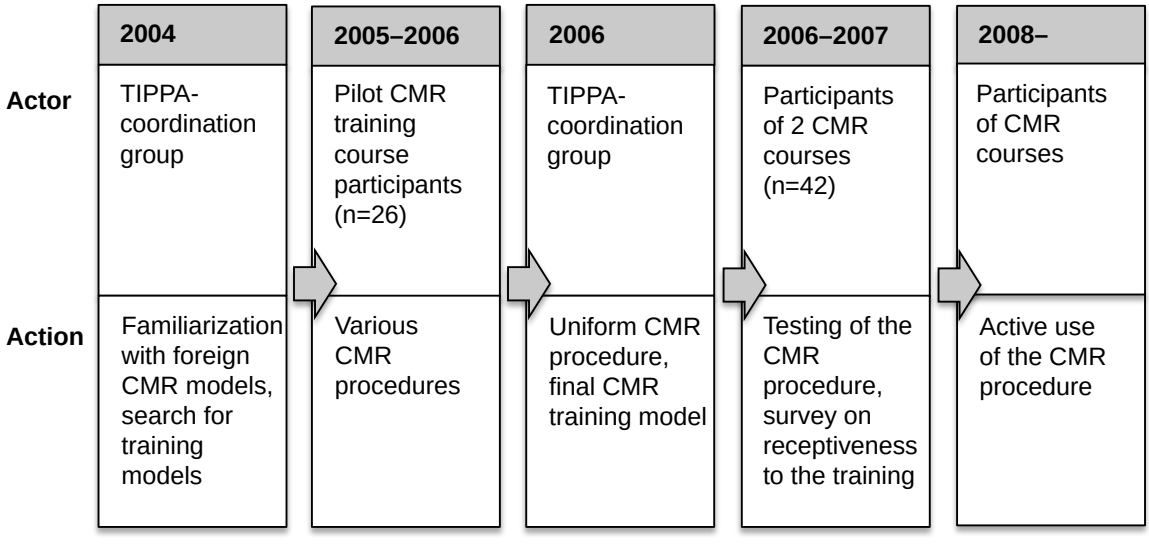

Figure 9 *Development of the CMR accreditation training and CMR procedure*

6.2.3 Participant Receptiveness to the CMR Accreditation Training (II)

The CMR training participants in Helsinki and Oulu in 2006–2007 were asked to evaluate the CMR training curriculum and their learning outcomes within a month after they completed the training. An Internet-based survey routinely used by the Centre for Training and Development, University of Eastern Finland (University of Kuopio at the time of this study) was used for this purpose. The survey instrument consisted of 3 sections with three types of questions (Table 20).

In addition, the participants were asked to estimate whether they were going to conduct CMRs in the future. The alternatives given for responses were: I will (the plans for the future already exist); I intend to continue the practice (the continuation will probably succeed); I'm still uncertain; and I will not conduct CMRs in my practice in the future.

Table 20. *Structure of the survey instrument to evaluate the CMR training curriculum (II)*

Section	Question type	Questions / issues addressed
I	5-point nominal rating scales (1=satisfactory, 5=outstanding)	Opinion on 1) Learning 2) Curriculum design 3) Teaching methods 4) Learning materials 5) Content validity of the assignments/group projects/examinations
II	Alternatives "yes", "possibly", "no"	1) Did the training meet your educational expectations and needs? 2) Would you recommend this training for your peers?
III	Open-ended questions	1) What factors facilitated your learning during this training? 2) What factors prevented or hampered your learning during this training? 3) What did you learn and how can you apply it to practice? 4) What ideas, comments and suggestions do you have for the improvement of the training?

6.2.4 Development of the CMR Documentation Forms (III)

The development of the CMR documentation forms involved four, partly overlapping, phases (Figure 10). The developed documents included: 1) A Referral and Patient Data Collection Form; 2) A Patient Interview Form; 3) A CMR Review Chart; 4) A CMR Case Report. In addition, a suitable Health-related Quality of Life (HRQoL) measure for the purposes of CMR was searched for.

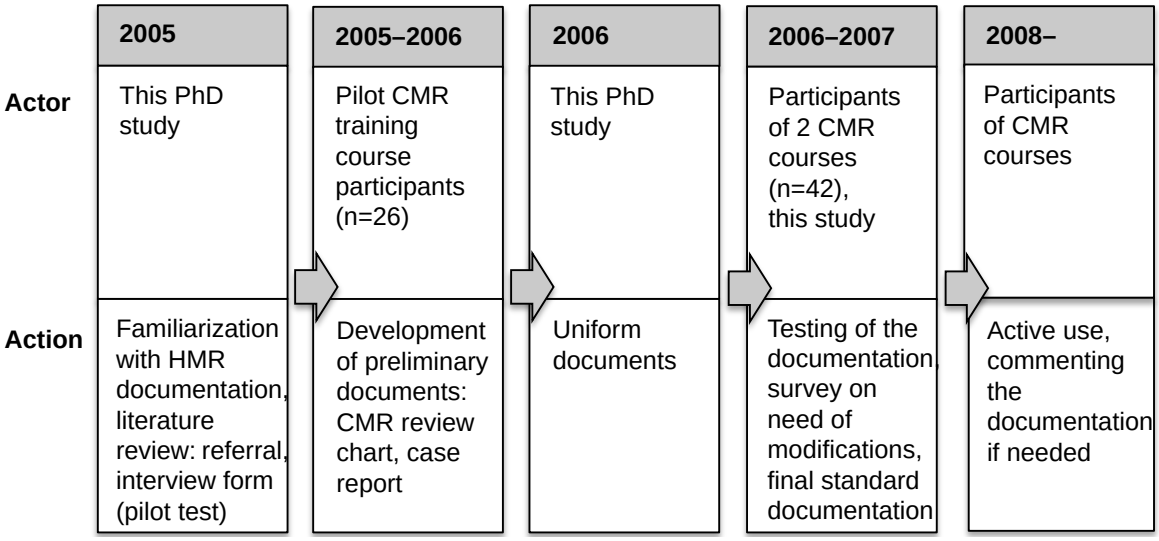

Figure 10 *Development of the CMR documentation*

In the first phase of the development of the CMR documentation the Australian HMR documentation (Australian Government 2011c) was familiarized with (Figure 10). In addition, a literature review was conducted to find information about issues that should be embedded in the CMR documentation forms. Based on this information a pilot CMR Interview Form was developed and tested among a pilot group of 9 home-health care patients aged >65 years in Lohja. The patients were asked to self-administer the form. A week later a face-to-face interview was conducted to compare the answers for accuracy and to test the usability of the form.

At the same time, the CMR pilot training participants developed for themselves the documentation they needed during CMR (Figure 10). The preliminary documents were collected after the training. They included a CMR Case Report and a CMR Review Chart. Various CMR charts were used to form a standard review chart. The standard CMR Case Report was developed by combining the various CMR case reports developed by the CMR pilot training participants, by using the HMR documentation for ideas and by utilizing the results of the abovementioned literature review.

The developed documentation forms were tested among CMR accreditation training participants in 2006–2007. When needed, the forms were modified based on their suggestions.

In addition to other documents, a literature search was conducted to find a suitable HRQoL measure to be used during CMR. HRQoL instruments can be either disease specific or generic (Kheir et al. 2004). For the purposes of CMR, which involves heterogeneous patient populations, a generic instrument is needed. Most CMR patients are elderly and the CMR interview may be of a long duration. Thus, the following were considered as necessary features for a suitable measure: 1) available in Finnish and in Swedish; 2) quick to administer; 3) simple language/wording in order to be suitable for elderly patients.

6.2.5 Survey on the Need to Modify the CMR Documentation (III)

The uniform CMR documentation format was tested by the CMR accreditation training participants in Helsinki and Oulu (Figure 10). At the end of the training the community pharmacist participants were asked to administer a survey to assess their opinions on the CMR documentation formats. The participants could send their responses as paper prints or via e-mail.

The survey instrument consisted of two parts. The first part had open-ended questions regarding the need to improve the CMR documentation (Table 21). The second part included a table with questions with three alternatives (yes, no, on some occasions) regarding the participant's opinion on the need: 1) to include each CMR documentation sheet in the CMR procedure in the future, and 2) to include suggested specific questions in the interview form (Table 22). In addition, there was space for free commenting at the end of the survey.

Table 21. *Open-ended questions of the survey instrument to address CMR accreditation training participants' opinions on the CMR documentation forms*

A. CMR referral and data collection form
1. Is this form necessary/needed or could you get the information regarding patient's medications and diagnoses easier some other way? Does completion of this form cause too much work for the physician? Is it enough just to tell the physician what patient data is needed for the review?
B. Patient interview form
1. Do you think that patient interview is useful/needed during CMR? Please, justify your opinion. 2. In your opinion, what issues are missing from the interview form? What information should be added? 3. Are there unnecessary questions in the interview form? Should certain questions be removed? 4. Questions regarding to anticholinergic adverse effects are included in the interview form. Is there a need to add questions regarding other adverse effects or symptoms, e.g., sedation, dizziness/vertigo, pain? What other symptoms do you consider necessary to ask about?
C. CMR case report
1. What issues are missing? What issues should be added? 2. Are there unnecessary sections (parts) in the report form? What and why?
D. CMR review chart
1. What is your opinion on the CMR review chart?

Table 22. *Questions in the survey instrument addressing CMR accreditation training participants' opinions on the CMR documentation forms*

Are the following documentation forms needed in the CMR procedure in the future			
	Yes	No	On some occasions
A. Referral form with patient clinical data			
B. Patient interview form			
Questions with potential for being added to the patient interview form			
Patient's weight and height			
Patient's health behaviors in general			
The following specific health behaviors:			
- smoking			
- alcohol consumption			
- diet			
- outdoor activities and exercise			
- sleeping/awake schedule and quality of sleep			
Existing questions:			
Questions regarding DRPs (#9.)[a]			
Questions regarding adherence (#10. and #11.)[a]			
Questions regarding stopping a drug (#12. and #13.)[a]			
Questions regarding wishes for changes in drug regimen (#14. and #15.)[a]			
Questions regarding anticholinergic adverse effects[a]			
3. A case report form			
4. CMR review chart			
[a] See Appendix 2			

6.2.6 Analysis of Drug-Related Problems (DRPs) Reported During CMR (IV)

DRPs were analyzed independently by two researchers from 121 CMR case reports. The CMR case report is long and may include documentation of non-significant findings to indicate that certain issues, e.g., drug-drug interactions (DDIs) have been checked during the CMR. In order to avoid overestimations, only the high-priority issues documented in the case report's separate section entitled "Most important findings and recommendations" were classified as DRPs. Drug-cost-related issues were commonly reported, but were not coded because the PCNE classification lacks such a DRP category.

The PCNE Classification for DRPs version 5.01 (Pharmaceutical Care Network Europe 2006) was used to code the DRPs, their causes and interventions resulting from the recognition of the DRP. Disagreements in classifications were resolved by discussion. Interventions were classified according to the physician's decisions at the case conference.

A few modifications were made to the original PCNE classification. A problem code "P3.5. Inappropriate dosing time or interval" was added to cover situations where daily drug dose was correct but the administration time was inappropriate (e.g., statins should be taken in the evening) or when the dosing intervals were wrong (e.g., nitrates taken without an appropriate washout period). Also two new cause codes were added: "C1.9. Treatment not discontinued/intervalled appropriately" was added, because in several cases drugs were used daily against recommendations for a long period of time (e.g., hypnotics), and none of the existing cause codes were suitable. Code "C4.11. Other patient-related cause" covered situations where the DRP was caused by some other action of the patient than that described in the alternatives of the PCNE classification. To specify the physicians' responses to the pharmacists' recommendations, two intervention classes "I1.6. Intervention proposed, carried out before case conference", and "I1.7. Intervention proposed, prescriber carried out other intervention", were added.

The medications related to the DRPs were classified using the Anatomical Therapeutic Chemical (ATC) classification system (WHO 2011). The results are presented on ATC level 3, unless only a single active ingredient is responsible for all DRPs in the drug class. If multible DRPs were reported for a single drug in a case report, only the DRP perceived to be clinically the most relevant was coded, unless (as in rare occasions) different recommendations for action were stated for each DRP. For example; the prescribed dose of an inhaled corticosteroid is too small, and in addition the patient cannot use the inhaler properly. The pharmacist recommends to increase the dose and to use a spacer devise. In this case, because there were two different recommendations, two DRPs were coded. In the case of some DRPs (drug-drug interactions, therapeutic duplication) two medications can be involved in one DRP.

6.3 Statistical Analyses

Frequencies of PIM users and percentage of the total outpatient population aged ≥65 years were counted from the SII data. The total reimbursement costs (€) for each PIM were summed and compared with the total reimbursement costs (direct drug costs) for all drugs reimbursed for persons aged ≥65 years.

The results of surveys were entered to Microsoft Excel. Descriptive statistics, i.e., frequencies, means and standard deviations were calculated, when appropriate. For some questions, also percentages of all respondents were calculated.

The DRP data were analyzed using SPSS version 16. Descriptive statistics, i.e., frequencies, percentages and means were counted. Comparisons between home-dwelling and assisted-living patient groups were made by independent sample *t*-test or Mann-Whitney *U* test, when appropriate. Pearson Chi-Square test was used to compare the distributions of DRPs between groups. P-values <0.05 were considered to be statistically significant.

7 Results

7.1 Use of Potentially Inappropriate Medications (PIMs) (I)

Of the non-institutionalized population aged ≥65 years in Finland (n=841 509), 91.8% (n=772 700) were dispensed reimbursable drugs in 2007. In total 123 545 individuals received reimbursements for PIMs according to the Beers criteria (Table 23). This corresponds to 14.7% of the non-institutionalized population aged ≥65 years in 2007.

Temazepam at doses >15 mg/day was clearly the most commonly reimbursed PIM with a prevalence of 4.4% (n=36 923) of the non-institutionalized population aged ≥65 years (Table 23). The next most common PIMs were products containing amitriptyline (2.0%; n=16 752), diazepam and combination products (1.8%; n=15 348), oral estrogens (1.8%; n=14 805) and short-acting dipyridamole (1.7%; n=14 280). More than one-third (36.9%; n=53 690) of the total PIM use (n=145 309) was associated with benzodiazepines, i.e., temazepam, diazepam and chlordiazepoxide (Table 23).

In 2007, the SII paid a total of 421 million euros for direct drug reimbursements for persons aged ≥65 years. The reimbursements for PIMs were 2.9 million euros, corresponding 0.7% of the total direct drug reimbursement costs for persons aged ≥65 years (Table 23).

Table 23. *Potentially inappropriate medication (PIM) use and drug reimbursements among non-institutionalized Finns aged ≥65 years (n = 841 509) in 2007*[a,b,c]

Potentially inappropriate drug	%	n	Reimbursement (€)
Temazepam, doses >15 mg/d[d]	4.4	36 923	574 872
Amitriptyline and combinations[d]	2.0	16 752	299 877
Diazepam and combinations[d]	1.8	15 348	155 850
Oral estrogens[d,e]	1.8	14 805	251 683
Dipyridamole, short acting[d]	1.7	14 280	491 489
Orphenadrine and combinations	1.5	12 533	65 659
Digoxin >0.125 mg/d (0.25 mg)	1.1	9 323	68 423
Doxepin[d]	0.5	4 249	114 491
Indomethacin[d]	0.5	4 050	45 949
Daily fluoxetine[d]	0.5	3 825	72 496
Oxybutynin, short acting[d]	0.4	3 479	132 500
Amiodarone	0.2	1 885	209 083
Carisoprodol (combination product)[d]	0.2	1 630	43 797
Ergot mesyloids	0.2	1 463	121 771
Chlordiazepoxide and combinations[d]	0.2	1 419	18 188
Nifedipine, short acting	0.1	1 120	58 767
Meprobamate (combination products)[d]	0.1	805	16 235
(Dextro)propoxyphene[d]	0.1	684	24 929
Disopyramide	0.1	663	77 870
Amphetamines and anorexic agents: sibutramine, dexamphetamine, methylphenidate, modafinil	0	73	23 321
Any of the above	14.7	123 545[f]	
Total		**145 309**	**2 867 250**

[a] Table excludes PIMs that were not reimbursable in Finland in 2007: triazolam, belladonna alkaloids, diphenhydramine, hydroxyzine, ferrous sulfate, bisacodyl, nitrofurantoin and clonidine.
[b] Table excludes lorazepam, oxazepam, alprazolam, naproxen and piroxicam because the dose used or duration of treatment could not be defined.
[c] Table excludes PIMs that were not available in outpatient care in Finland in 2007
[d] Some small packages or product brands were not reimbursable.
[e] No information on concomitant progesterone therapy.
[f] One individual may have used several PIMs.

Reproduced from [Leikola S, Dimitrow M, Lyles A, et al. Potentially inappropriate medication use among Finnish non-institutionalized people aged ≥65 years. A register-based, cross-sectional, national study. Drugs Aging 2011;28(3):227-236] with permission from Adis, a Wolters Kluwer business (© Adis Data Information BV [2011]. All rights reserved.)

7.2 CMR Accreditation Training and Participant Satisfaction (II)

7.2.1 CMR Accreditation Training

The TIPPA Coordination Group defined the aims of the CMR accreditation training as follows: 1) to support participant's professional development to acquire sufficient clinical skills and knowledge to conduct CMRs; 2) to establish collaboration needed for CMR with other health care professionals, particularly with local GPs; and 3) to create the CMR procedure applicable to local circumstances.

The CMR curriculum is designed to last for three semesters, 1.5 years, and corresponds to 35 European Credit Transfer System (ECTS) credits (1 credit corresponds to 26.7 hours of student work). The training is intended to be completed while working. 20–25 pharmacists are accepted to participate in one training course. Both hospital and community pharmacists attend the same training in order to facilitate learning from each others' skills and experience. Accreditation from the professional organizations (Association of Finnish Pharmacies and The Finnish Pharmacists' Association) is gained by completing the training course and preparing a portfolio for the TIPPA Coordination Group. The portfolio needs to reflect the students' professional and personal growth from the start of the training to its completion and to address the participants' plans for the future.

Structure of the Curriculum

The curriculum includes both face-to-face learning and distance learning and it utilizes various teaching methods. These methods include written assignments, e.g., essays and learning diaries, expert lectures, working in small groups, and most importantly, collaboratively conducting actual CMRs.

Structurally, the curriculum consists of ten two-day seminars and independent distance learning in-between, some of which take place in an e-learning environment (Table 24). Before each seminar session participants need to complete assignments, including review of specific reading materials. Because reflection and self-assessment are strongly involved throughout the training, educational needs and goals are described in an essay prior to the first seminar and progress is evaluated by written learning diaries completed after each seminar session (Table 24). The seminar days include lectures by leading national experts on different appropriate fields, as well as small group sessions. Small groups of 4–6 people are formed at the beginning of the training in order to facilitate interaction between students. Hospital pharmacists and community pharmacists are in separate groups in order to achieve optimal peer support. Each small group is guided by a tutor who is accredited to conduct CMRs. The small groups have their own discussion forums in the e-learning environment and they meet during each seminar day to follow everyone's progress in implementing the CMR procedure in their local health care environment, to discuss CMR patient cases and to perform long-term projects on e.g., care guidelines.

Distance learning consists of the following elements: 1) multidisciplinary networking and developing of a local CMR procedure that aim to permanent collaboration; 2) learning by reviewing actual patient cases selected from the pharmacist's own practice; 3) theoretical studies and literature; 4) working in an e-learning environment (Moodle). Moodle is an interactive discussion forum where participants can discuss their patient cases, solve problems and share ideas and knowledge. Secondly, Moodle is a template for almost all course-related materials including timetables, assignments, CMR forms and tools, reading assignments and instructors' PowerPoint presentations. A majority of the completed assignments are submitted to the discussion areas so that all participants can learn from them.

Core Contents of the Curriculum

The CMR curriculum consists of five modules continuing throughout the entire training (Figure 11). The case studies integrate the modules by combining different kind of knowledge needed in CMR.

The Multidisciplinary Collaboration module is the most time intensive, with assignments intended to guide the participants in creating a permanent CMR collaboration within their local health care environment. Conducting actual CMRs is a crucial part of this module. Each participant needs to complete 5–10 reviews during the training. In addition, the cases are presented and discussed in small groups at every seminar session and brought to the e-learning environment to support the learning of others. While conducting and discussing the CMRs, the participants utilize in practice the theoretical knowledge obtained from other modules.

The Clinical Pharmacy and Pharmacotherapy module includes elements of pharmacotherapy, pharmacokinetics, geriatrics, etiology and pathology, psychology, nursing science, and ethics. Clinical chemistry, i.e., the interpretation of laboratory results, is also included. All topics are approached from the medication review perspective. Thus, evidence-based treatment of common diseases and the effects that, for example, aging, renal failure, and polypharmacy have on pharmacotherapy are essential topics in this module.

The Rational Pharmacotherapy module covers the concepts of rational use of medicines and patient safety, drug-related problems, adherence, factors influencing medication use and selection, and trends in pharmacotherapy and ethics. Evidence-based Finnish Current Care Guidelines are studied and the knowledge gained is used in conducting CMRs.

The CMR Tools module is intended to acquaint participants with the CMR documentation forms and their theoretical background, different databases and reliable information sources that can be used when conducting CMRs. Development, marketing, and pricing of CMR services are crucial assignments in the Tools module. The participants study written materials on communication skills and interview techniques and then work in small groups with a communications professional to practice their skills and techniques.

Optional studies can be chosen to complete knowledge on relevant topics but need to be related to CMR and include a reflective component, e.g., a written report. They can be performed as literature reviews, conventional examinations, short lecture-based courses, or any other way producing CMR-relevant learning outcomes.

Table 24. *CMR Curriculum Design*

SEMINARS (2 days each)	**LECTURE TOPICS (The whole training group, n=20–25)**		**SMALL GROUP WORKING SESSIONS (n=4–6)**	
FIRST SEMESTER (6 months) Preliminary essay: Me in the beginning of the studies				
I Initial meeting	Introductions Principles of constructive adult learning	Rational use of medicines	Introductions	Patient cases presented by the tutor
II	Multidisciplinary collaboration	CMR procedure	Building of multidisciplinary collaboration	Case studies (medication lists)
III	Adherence Medicines management in the elderly	CMR documentation (theory, tools)	Current Care Guidelines	Case studies (actual cases)
SECOND SEMESTER (6 months) Learning diary of the first semester				
IV	Communication and interview skills		Current Care Guidelines Home interview rehearsal (role play)	Case studies (actual cases)
V	Clinical chemistry		Current Care Guidelines	Case studies (actual cases)
VI	Epidemiology	Information sources	Case studies (actual cases)	
THIRD SEMESTER (6 months) Learning diary of the second semester				
VII	Alzheimer's disease and other cognitive disorders	Introduction to portfolio	Case studies (actual cases)	
VIII Healthcare partners	Health policy issues in CMR Foreign CMR practices		Case studies (actual cases) in multiprofessional groups	
IX Employers	Local CMR procedure; pricing; marketing		Case studies (actual cases)	
X Final meeting	Local CMR procedure	Evaluation of the training and meeting the learning objectives	Case studies (actual cases)	Peer evaluation
END OF TRAINING: Learning diary of the third semester, final essay				

▼

PORTFOLIO SUBMISSION (2 months)

▼

ACCREDITATION

▼

Multiprofessional collaboration, conducting CMRs, continuing learning, portfolio updating (5 years)

▼

REACCREDITATION

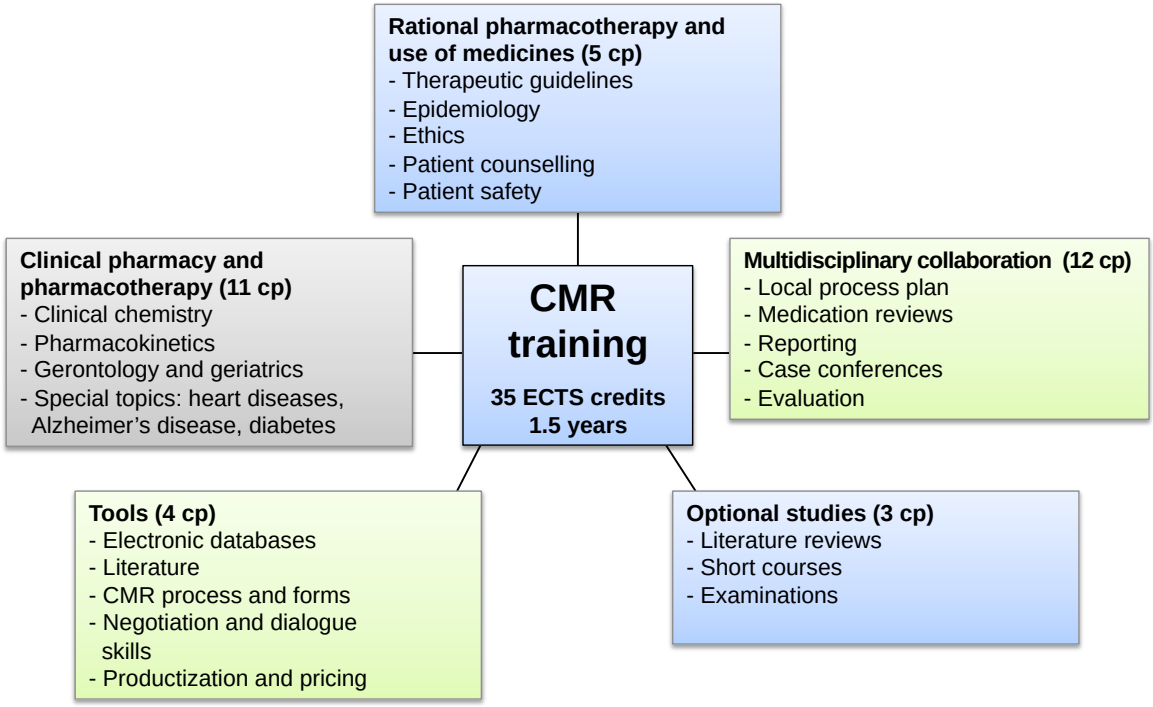

Figure 11 *Core contents of the CMR accreditation training (35 ECTS credits (cp), 1.5 years).*

7.2.2 Participant Satisfaction on CMR Accreditation Training

A majority (92.1%, n=35) of the pharmacists who completed the CMR accreditation training in 2006–2007 perceived that the course met their educational needs. Even more (94.7%; n=36) would recommend the training to their peers. The mean score for different survey statements assessing satisfaction on training was 4.5 ± 0.7 (Table 25). The highest ratings were given to learning (4.6 ± 0.7) and curriculum design (4.6 ± 0.5).

Table 25. *Pharmacists' (n=38) perceptions of the CMR accreditation training right after completing it (1 = poor to 5 = outstanding)*

Variable evaluated	Mean score ± SD (range)
Learning	4.6 ± 0.7 (2–5)
Curriculum design	4.6 ± 0.5 (4–5)
Teaching methods	4.4 ± 0.7 (3–5)
Learning materials	4.4 ± 0.6 (3–5)
Content validity of assignments/group works/examinations	4.3 ± 0.7 (3–5)
Mean of all statements	**4.5 ± 0.7**

A majority (83.3%, n=35) of the training participants responded to the open-ended questions concerning factors which facilitated, prevented or hampered their learning (Figure 12). The most commonly mentioned facilitating factors could be grouped under nine main themes (Figure 12). Almost all of the respondents (91.4%, n=32) mentioned that the small group format (42.9%, n=15), working in groups (28.6%, n=10), or other participants (20.0%, n=7) had improved their learning. The hampering factors were grouped under six main themes (Figure 12). The most commonly mentioned preventive or hampering factors were “lack of time” and ”busyness” (40.0%, n=14) and job constraints (37.1%, n=13) such as busyness or lack of support at the workplace.

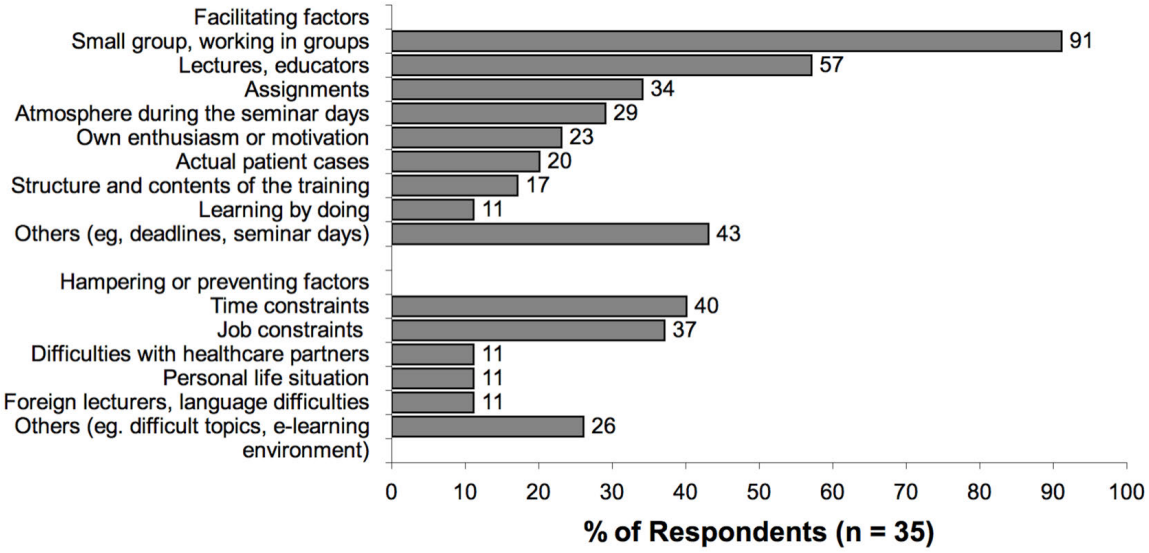

Figure 12 *CMR training participants’ opinions on factors facilitating and hampering learning during the CMR accreditation training (content analysis of open-ended questions)*

The most common response (response rate 85.7%, n=36) to the question “What did you learn and how can you apply it to practice?” was simply “I learned a lot” (36.1%, n=13). Ten respondents (27.8%) mentioned issues related to pharmacology or pharmacotherapy. Both multidisciplinary collaboration and development of CMR procedure were mentioned by 8 participants (22.2%), geriatric pharmacotherapy by 6 (16.7%), and interpretation of laboratory test values by 5 (13.9%). Several participants mentioned “broader perspective” or “seeing things as a whole” (16.7%, n=6) or application of existing knowledge (11.1%, n=4). Half of the respondents (n=18) mentioned the learning was useful in everyday work regardless of whether it involved conducting CMRs.

Twenty-nine participants (69.0%) suggested ideas to improve the training. Even though working in small groups was seen as a useful way of learning, some of the respondents wished for more communication between all participants (13.8%, n=4) or occasional mixing of tutor groups for a broader perspective (10.3%, n=3). Six respondents (20.7%) wished for additional annual training days. The development of CMR services

was seen as difficult and time consuming, so a few students (10.3%, n=3) wanted that to be started at an earlier phase of the training and an additional 3 (10.3%) wanted a lecture on an operational local CMR practice.

Most of the respondents (68.4%, n=26) planned to conduct CMRs in the future. Five (13.2%) answered "I will (the plans for the future already exist)" and 21 (55.3%) "I intend to continue the practice". Eleven respondents (28.9%) were still uncertain. Only 1 respondent who had discontinued her studies indicated that she will not conduct CMRs in the future. The respondents mentioned the following barriers to conducting CMRs in the future: financing (13.2%, n=5); still unclear, whether the employer wants to provide CMR services (8.0%, n=3); and development of the local CMR procedure is still under way (5.3%, n=2).

7.3 CMR Procedure and Documentation (III)

7.3.1 CMR Procedure

The intensive development phase resulted in a comprehensive medication review procedure which requires access to clinical patient information, a home visit with a patient interview, and a case conference with the collaborative physician. The procedure covers four main dimensions critical for safe and appropriate pharmacotherapy for the elderly: Aging and Safety; Co-Morbidities; Polypharmacy; and Adherence (Figure 13). The measures and documentation of the CMR procedure are designed to reflect these dimensions.

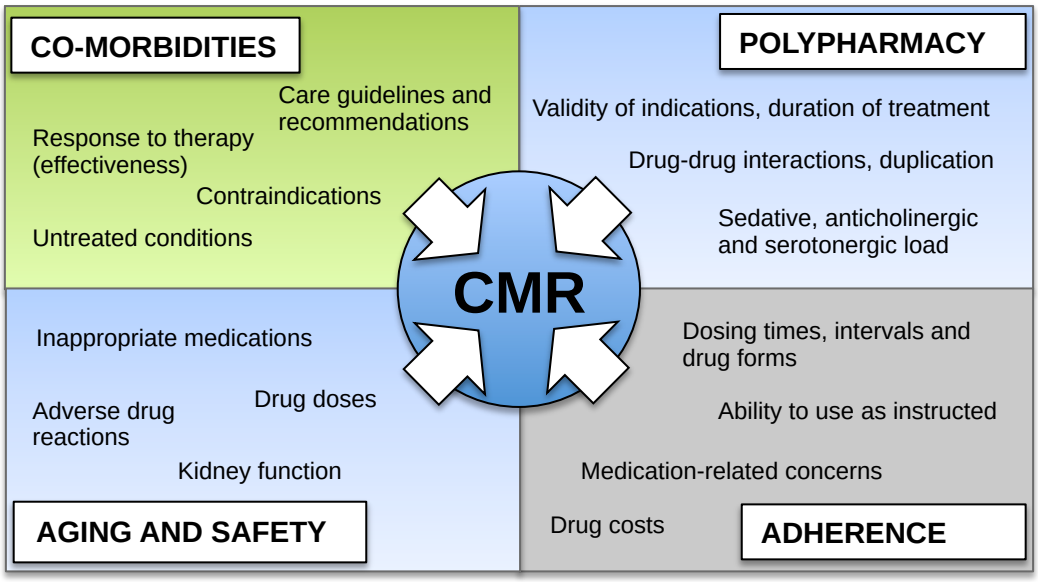

Figure 13 *Four dimensions covered by the CMR procedure to ascertain safe and appropriate pharmacotherapy among elderly patients*

The phases of the CMR procedure follow the structure of the HMR in Australia (Sorensen et al. 2004) and MTM in the US (APhA and NACDS 2008) (Figure 14). The CMR is usually initiated by the physician on the basis of potential problems in the patient's drug treatment (Figure 14: Phase 1). Other caregivers can actively suggest CMR for a particular patient. The criteria for conducting CMRs are currently set locally in Finland. After receiving a written consent from the patient, the collaborative physician provides the pharmacist with sufficient patient information, including medication lists, diagnoses, laboratory test results and other relevant data needed in conducting CMR (Appendix 3).

After becoming acquainted with the clinical patient information the pharmacist visits the patient at home and conducts a face-to-face interview (Figure 14: Phase 2) by using the Interview Form (Appendix 2). The aims of the interview are 1) to complete and update medication lists to reflect the patient's actual drug use, including OTC drugs, herbal products and complementary medicines; 2) to recognize various clinical and practical DRPs, including underreported adverse drug effects (Lampela et al. 2007); 3) to gather monitoring data; 4) to assess behaviors and living conditions that may influence medicine use and adherence; 5) to measure HRQoL. In addition, the patient is advised on his/her medication use throughout the interview. If an interview with the patient is not possible, or if additional discussions are considered useful, the pharmacist may consult nurses or other caretakers.

Like the patient interview, the actual review of medications (Figure 14: Phase 3) also follows a literature-based, structured case report format (Appendix 4). The format is designed to cover the previously mentioned four dimensions that are crucial in assuring rational pharmacotherapy among the elderly patients (Figure 13). In addition to having good basic knowledge on pharmacology based on their degree and additional knowledge on elderly pharmacotherapy gained through the CMR accreditation training, the pharmacists use several resources and tools while conducting the review. These include the national current care and geriatric pharmacotherapy guidelines (Kivelä and Räihä 2007, www.kaypahoito.fi), criteria for potentially inappropriate medications for the aged (Fick et al. 2003, Socialstyrelsen 2010, Fimea 2011), an electronic drug-drug interaction screening database (e.g., Lääkeinteraktiot SFINX), and a database to select appropriate drugs and doses for patients with kidney failure (Renbase 2011). Special attention is paid to potentially harmful sedative load (Linjakumpu et al. 2003), and to excessive use of serotonergic and anticholinergic drugs (Hilmer et al. 2007, Looper 2007).

The CMR case report with findings and recommendations is discussed with the physician in a face-to-face case conference (Figure 14: Phase 4). It is desirable that other caregivers, e.g., a nurse or a family member, possibly also the patient, also participate in the conversation to ensure the proper implementation of changes in practice. The physician is in charge of all medical decisions. After there is an agreement on the actions and follow-up, the pharmacist documents all decisions on the CMR case report. The patient and caretakers can be provided with a shortened version of the report.

A follow-up home visit focuses on identification of current medications, ascertaining that the agreed changes have been implemented and DRPs resolved, as well as re-evaluation of the patient's HRQoL. The follow-up is important, because interventions with

a follow-up are found more likely to improve adherence (George et al. 2008). Usually the follow-up occurs three months after the case conference but different intervals may be agreed on based on the patient's individual needs.

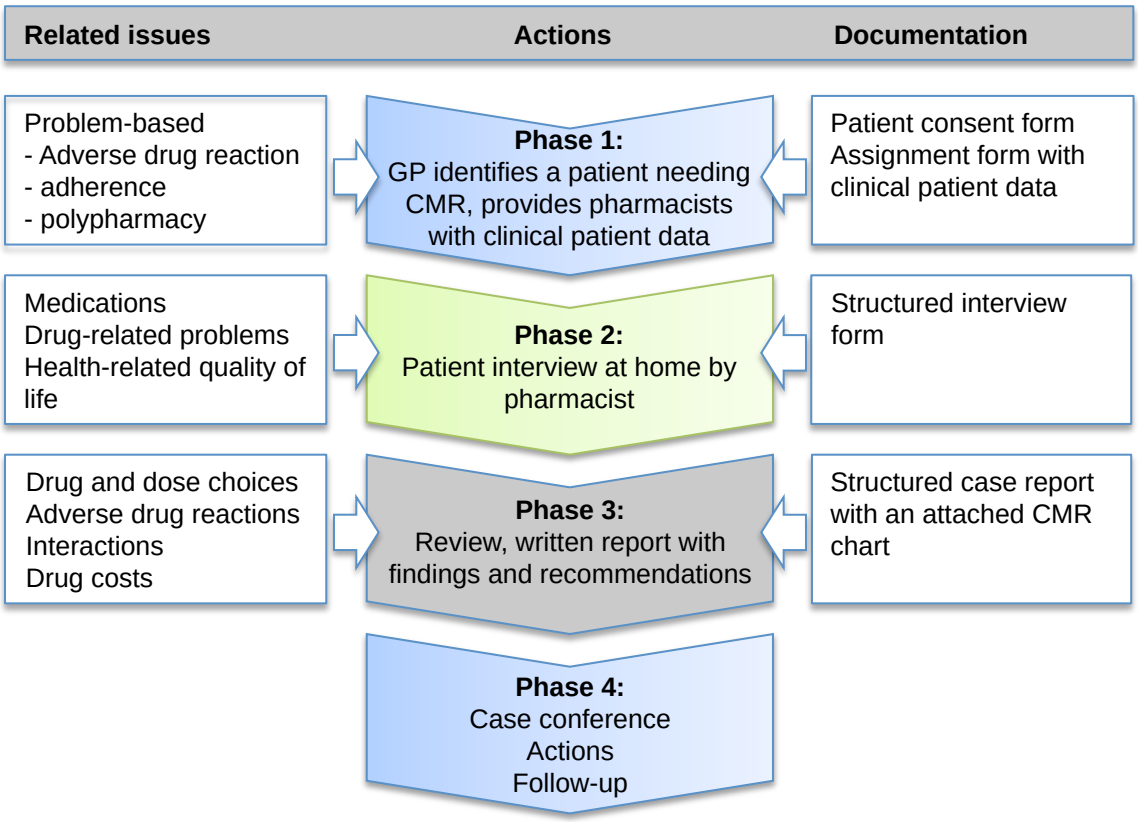

Figure 14 *Phases of the CMR procedure and related documentation forms*

7.3.2 CMR Documentation

CMR Referral Form

The Australian HMR documentation that was used included a referral form for physicians to refer patients to HMR and to provide relevant patient information to pharmacists, and a Medication Management Plan (Australian Government 2011c, Commonwealth Department of Health and Aged Care 2011). The developed CMR Referral and Patient Data Collection Form (Appendix 3) resembles the corresponding Australian form.

A majority (70.4%, n=19) of the accreditation training participants in 2006–2007 who responded to the survey on the development needs of the CMR documentation forms indicated that the CMR Referral Form is needed in the CMR procedure in the future at least in some occasions (Table 26). Still, in the open-ended questions 17 pharmacists

(63.3%) stated, that prints of medical records were a more efficient, easy and/or reliable way to acquire patient data. However, some indicated that the Referral Form may be useful if completed by the pharmacist to gather relevant information from patient records (n=3) or to be used as a checklist that all relevant data has been gathered (n=2). As a result, the CMR Referral Form is an optional document that can be used during the procedure if considered to be useful.

Table 26. *CMR training participants' opinions on the need to include CMR documents and specific interview question in the CMR procedure (n=27; response rate 84.4%)*

Are the following documentation forms needed in the CMR procedure in the future			
	Yes % (n)	**No % (n)**	**On some occasions % (n)**
A. Referral form with patient clinical data	29.6 (8)	29.6 (8)	40.7 (11)
B. Patient interview form	92.6 (25)	0	7.4 (2)
Questions with potential for being added to the patient interview form			
Patient's weight and height	88.9 (24)	3.7 (1)	7.4 (2)
Patient's health behaviors in general	92.6 (25)	0	7.4 (2)
The following specific health behaviors:			
- smoking	88.9 (24)	0	7.4 (2)
- alcohol consumption	92.6 (25)	0	7.4 (2)
- diet	96.3 (26)	0	3.7 (1)
- outdoor activities and exercise	85.2 (23)	0	14.8 (4)
- sleeping/awake schedule and quality of sleep	88.9 (24)	0	11.1 (3)
Existing questions:			
Questions regarding DRPs (#9.)[a]	88.9 (24)	3.7 (1)	7.4 (2)
Questions regarding adherence (#10. and #11.)[a]	81.5 (22)	7.4 (2)	11.1 (3)
Questions regarding stopping a drug (#12. and #13.)[a]	88.9 (24)	3.7 (1)	7.4 (2)
Questions regarding wishes for changes in drug regimen (#14. and #15.)[a]	88.9 (24)	3.7 (1)	7.4 (2)
Questions regarding anticholinergic adverse effects[a]	92.6 (25)	0	7.4 (2)
C. A case report form	100 (27)	0	0
D. CMR review chart	85.2 (23)	7.4 (2)	7.4 (2)
[a] See Appendix 2			

CMR Interview Form

The literature review for this thesis provided the theoretical basis of the CMR Interview Form (Table 27). Because pharmaceutical care and medication review models aim to recognize, prevent and resolve DRPs, it was concluded that the CMR documentation should ascertain that all relevant DRPs are addressed during CMR. A literature review on DRP classification systems by van Mil et al. (2004) was used to identify potential DRPs to be included in the CMR documentation. Based on an examination of the various DRP classifications (van Mil et al. 2004), it was concluded that classification by Cipolle et al. (2004) has several advantages for the purposes of CMR. It addresses comprehensively clinical DRPs, such as untreated conditions, drug use without valid indication and inappropriate doses (Table 6). Such issues can be addressed during CMR because the pharmacist has access to diagnostic data and laboratory test results. As a disadvantage, the DRP classes of the CMS system are sparse and many issues that need to be checked during CMR to ascertain appropriateness of pharmacotherapy, e.g., drug-drug interactions, duration of therapy, practical difficulties, and drug expenses are causes of DRPs in the CMS system. Lack of classification system for these causes impaired the usability of the CMS system when specific questions for CMR patient interview were developed.

The DRP classification by Westerlund et al. (1999a,b, 2002), on the other hand, considers several practical problems related to drug administration, such as difficulties in swallowing tablets/capsules and opening containers (Table 7). It also pays attention to the patients' knowledge of their medications. Such DRPs may unnecessarily complicate taking drugs appropriately but are usually easily resolved by CMRs, e.g., by patient counseling or changing the drug formulation. On the other hand, the Westerlund classification has disadvantages that impair its usability during CMR. It lacks several clinical DRPs that are important during CMR, e.g., untreated indications and unnecessary drug therapy. However, if combined, these two DRP classification systems address most domains of inappropriateness of pharmacotherapy and thus, all DRPs from both were embedded in the CMR Interview Form (Table 27).

The PCNE Classification for DRPs (Pharmaceutical Care Network Europe Foundation 2010, Appendix 1) allows classification of causes for DRPs, interventions and even outcomes of the intervention. The subdomains of the DRPs and causes are detailed, so classification of various upcoming issues are likely to succeed. On the other hand, due too the great number of subgroups interrater variability may be poor. A positive feature in the PCNE classification in CMR is the possibility to also classify potential DRPs, i.e., the risks of pharmacotherapy that the pharmacist may recognize and aim to prevent. Currently, the PCNE DRP classification version 6.2 (PCNE 2010, Appendix 1) is used by accredited pharmacists when the findings and outcomes of CMRs are documented for research purposes and it can be used as an evidence of the effects of CMR by individual CMR pharmacists.

In addition to DRPs, some more specific issues were included in the CMR Interview Form. Based on published studies elderly patients commonly use OTC drugs, natural products and complementary medicines and physicians may be unaware of this and lack a complete picture of the drugs that are actually used (Barat et al. 2000, Frank et al. 2001,

Pharand et al. 2003, Kaunisvesi 2005). This is important because OTC medications, dietary supplements and natural products may interact with pharmacotherapy (Hoblyn and Brooks 2005, Qato et al. 2008). For these reasons, the first part of the Interview Form was developed to focus on revealing patient's actual drug use (Table 27).

Anticholinergic adverse effects are known to be harmful for elderly patients, because they may lead to impaired cognitive and physical function (Hilmer et al. 2007, Landi et al. 2007b, Cao et al. 2008). The Udvalg for Kliniske Undersøgelser (UKU) Side-effect Rating Scale was developed for physicians to assess unwanted effects of psychotropic drugs, including anticholinergic effects (Lingjaerde et al. 1987). The scale has in total 7 questions relating to anticholinergic adverse effects. Of these, three i.e., constipation, dryness of mouth and urinary disturbances are easy for the patient to self-report and simple for the pharmacist to interpret. Thus, these 3 questions were included in the CMR Interview Form.

The pilot testing of the literature-based preliminary interview form (Questions marked with * in Appendix 2) among home health care patients (n=9) revealed no need to change the form. However, it became evident that the form was not suitable for self-administration by the patients as 4 of the 9 patients were entirely unable to complete it.

Table 27. *Literature-based evidence for the developed CMR Interview Form*

DISCUSSED ISSUE	THEORETICAL BASIS
Medication management	
Number of physicians involved in patient's care	Number of prescribing physicians is an independent risk factor for adverse drug events among elderly outpatients (Green et al. 2007).
Way of taking medicines (self from original containers, dose dispensing device, automated dose dispensing, help from relatives or caregivers)	DRP/ Non-compliance[a] DRP/ Difficulty opening drug container[b], other practical problem[b]
Medication use	
Prescription and OTC medications, natural products, dietary supplements	Discrepancies between the medication lists of physicians and actual drug use are common, and may result in drug interactions and adverse events (Barat et al. 2000, Frank et al. 2001, Pharand et al. 2003). OTC medications, dietary supplements and natural products may interact with pharmacotherapy (Hoblyn and Brooks 2005, Hu et al. 2005).
Doses, dosing times, dosing intervals	DRP/Unnecessary drug therapy[a] DRP/Too low dosage[a], too high dosage[a] DRP/Overuse[b], underuse[b] DRP/ Non-compliance[a]
Medication-related knowledge	DRP/Uncertainty about the indication for the drug[b]
Drug-related problems	
Practical difficulties (ability to use as instructed)	DRP/Difficulty swallowing tablet/capsule[b], difficulty opening drug container[b], other practical problem[b]
Concerns related to drug costs	DRP/Non-compliance[a]
Adherence (use against instructions, discontinuation of treatment, forgetfulness)[c]	DRP/Non-compliance[a]
Adverse drug reactions (including questions concerning dizziness, falls and anticholinergic side-effects constipation[d], dryness of mouth[d], and urinary disturbances[d])	DRP/Adverse drug reaction[a,b] Elderly people underreport adverse effects to their physicians (Lampela et al. 2007). Anticholinergic adverse effects can be very harmful to the elderly, because they may lead to impaired cognitive and physical function (Hilmer et al. 2007, Landi et al. 2007b, Cao et al. 2008).
Undertreatment or suboptimal treatment results (as defined by the patient), including pain, mood, sleeping disorder	DRP/Need for additional therapy[a], ineffective drug[a] Undertreatment of pain in community-dwelling older people is common (Pitkälä et al. 2002a).
Monitoring	
Laboratory test results and other measurements available at home (e.g., blood glucose, blood pressure)	DRP/ Ineffective drug[a], therapy failure[b] DRP/Need for additional therapy[a] Many adverse drug events that result in hospitalization could be prevented by better monitoring (Thomsen et al. 2007). More recent measurements by e.g., visiting nurses may be available at home.

DISCUSSED ISSUE	THEORETICAL BASIS
Health habits and related issues	
Weight, height	Weight is needed to count the Body Mass Index (BMI) and glomerular filtration rate to define kidney function.
Smoking, alcohol consumption	Smoking and alcohol consumption may have clinically significant interactions with drugs (Weathermon and Crabb 1999, Kroon 2007).
Nutrition	Quality of nutrition affects e.g., need for calcium, iron and vitamin supplements.
Outdoor activity, exercise	Exposure to sunlight affects the need for supplementary vitamin D (Holick and Chen 2008).

DRP=Drug-related problem, OTC=over-the-counter
[a] Based on DRP Classification System by Cipolle et al. (2004)
[b] Based on the DRP Classification System by Westerlund et al. (1999 a,b, 2001)
[c] Morisky adherence scale as an attachment (Morisky et al. 1986)
[d] Adopted from Udvalg for Kliniske Undersøgelser (UKU) side-effect rating scale (Lingjaerde et al. 1987)

Almost all (96.3%, n=26) of the accreditation training participants in 2006–2007 who responded to the survey indicated that the patient interview is an important part of the CMR procedure. Only one pharmacist who conducted CMRs in an assisted living setting answered that the patient interview was not useful, as the collaborating nurses provided more reliable information. However, she indicted that the interview might be useful among home-dwelling patients. Several pharmacists mentioned that the interview revealed important issues that were not evident in the patient records or known by the physician (55.6%; n=15). One respondent even mentioned that the interview would be useful among demented patients, because potentially dangerous or outdated medications can be removed from closets. Several respondents (n=6) mentioned that it is crucial to understand the patient's opinions regarding their pharmacotherapy and taking of medicines. A few (n=5) pointed out the importance of giving advice and improving adherence.

All respondents indicated that the Interview Form is needed in the CMR procedure (Table 26). In the open-ended question regarding need to add new questions to the Interview Form, several suggestions (n=18) arose, but only health habits, such as smoking and diet (n=10), weight (n=7), pain (n=3), laboratory test results (n=2), sleep (n=2), dizziness (n=2), fatigue (n=2) and itching (n=2) were mentioned by more than one participant. The first 6 of these were added to the Interview Form (Appendix 2).

When specifically asked if questions regarding some other symptoms needed to be added to the Interview Form, the examples presented in the survey (Table 21), i.e., pain (n=22), dizziness (n=25) and issues relating to quality of sleep, like insomnia, fatigue and other sleeping disorders (n=16) were mentioned by several respondents. These were added to the Interview Form by formulating the questions similarly to the ones in the UKU Side-effect Rating Scale or the version of it used for patient self-administration (Lingjaerde et al. 1987, Lindström et al. 2001; Appendix 2). Falls, nausea and stomach ache were suggested to be added to the Interview Form by two participants, and palpitations, pruritus, headache, arrhythmias and memory disturbances by one each. Of these, only falls were added, because they are considered to be a severe and common adverse effect among the aged, which may often be prevented by intervening in pharmacotherapy (Kivelä and Räihä 2007).

Almost all of the respondents considered useful to include questions about weight, height and health habits in the Interview Form (Table 26). Thus, questions on these topics were added to the Interview Form (Appendix 2).

With regard to need to remove existing questions from the Interview Form, 48.1% (n=13) stated “No”. No individual question to be removed was mentioned by more than one respondent, but 5 participants expressed the need to condense the text or to develop a simpler version to be used after the CMR training. Also in alternative questions the majority of the CMR training participants responded, that the existing questions of the CMR Interview Form are needed also in the future (Table 26). As a result, no questions from the preliminary form were removed, but the form was simplified (Appendix 2).

CMR Case Report Form

The developed standard CMR Case Report Form (Appendix 4) follows the structure of the CMR patient interview and the same DRPs (Westerlund et al. 1999a,b, Cipolle et al. 2004) are also included in the Report.

All survey respondents indicated that the CMR Case Report is needed in the CMR procedure (Table 26). In open-ended questions the pharmacists suggested several issues that should be added to the report. These included e.g., a section documenting follow-up findings (n=7), Body Mass Index (n=2), Glomerular Filtration Rate (GFR) formula (n=2), and space for physician’s comments (n=2) and laboratory test results (n=1). All of these were added (Appendix 4). A few respondents wanted to remove the list of used drugs (n=6) and the table to indicate the drug costs before and after CMR (n=4). During CMR, pharmacists can remove these sections from the report if they consider them unnecessary.

CMR Review Chart

Integration of various preliminary CMR Review Charts developed by pilot CMR accreditation training participants resulted in a standard Review Chart Form (Appendix 5). All used medications and their effects on e.g., CYP-enzymes, blood pressure and serum electrolytes can be collected on the form. The aim of the Chart is to facilitate review of medications with regard to their effects during concomitant use, for example pharmacokinetic and pharmacodynamic interactions as well as sedative, anticholinergic and serotonergic drug load.

Of the CMR training participants in 2006–2007 who responded to the survey, 92.6% (n=25) indicated that the CMR Review Chart is needed in the CMR procedure at least occasionally (Table 26). In the open-ended questions more than half (59.3%, n=16) of the pharmacists stated the CMR Review Chart to be “OK” or “fine”. Some (n=7) answered it to be otherwise fine, but too laborious to fill in, or it was regarded to be useful in the beginning when the pharmacist learns to conduct CMRs. Thus, the review chart remains in the CMR procedure in its preliminary form.

Health-Related Quality of Life Measure for CMR

Based on the literature search to find a suitable HRQoL measure to be used during CMR, six generic HRQoL measures with a Finnish and Swedish translation were found (Figure 15). For SF-12 (Ware et al. 1996) no published studies regarding validation of the Finnish translation could not be found, and thus it was excluded. Of the remaining measures, the EuroQol (EQ-5D; Brooks 1996, Appendix 6) was considered to be the most suitable for CMR, because of its superior simplicity and quick administration time. Also, its suitability for elderly patients is well documented (Tidermark et al. 2003, Holland et al. 2004).

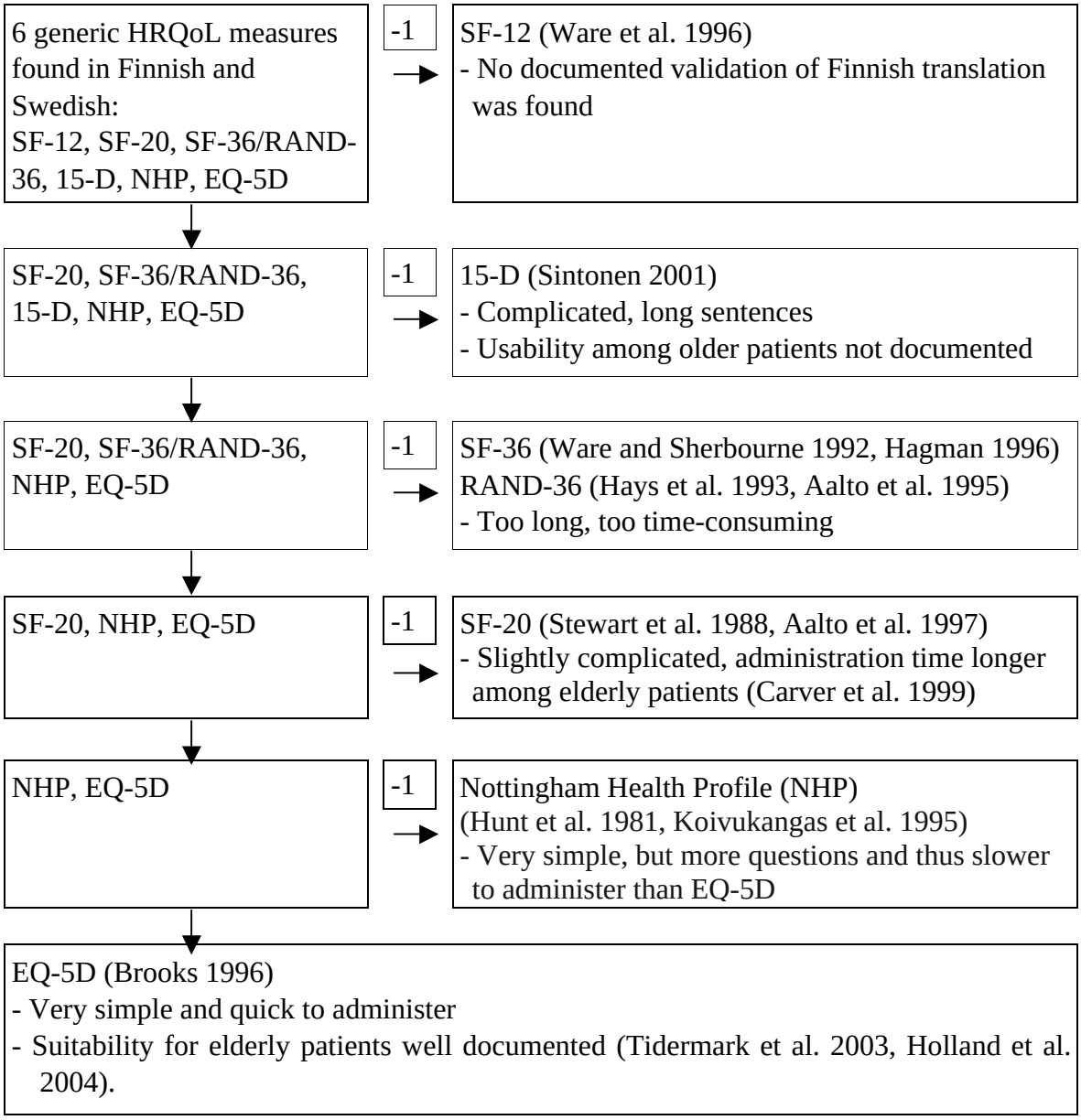

Figure 15 *Selection of suitable Health-Related Quality of Life (HRQoL) measure for CMR*

7.4 Drug-Related Problems Reported During CMR (IV)

The community pharmacists taking accreditation training in 2006–2007 reported altogether 785 DRPs, an average of 6.5 per patient. Mean number of DRPs was higher among home-dwelling patients (7.2), than among those in the assisted-living setting (5.5) (p=0.014) but the DRPs were similar in nature. Inappropriate drug choices were the most common DRPs (n=136; 17.3% of DRPs), they most often involved hypnotics and sedatives (Table 28). Indications with no prescribed drugs were the second most common DRPs (n=125; 15.9%) and involved most often calcium supplements, lipid-lowering drugs and ACE-inhibitors.

Causes of DRPs were most often related to selection of drug or dose (n=623; 79.4% of DRPs) (Table 29). Of these, the most common was inappropriate drug selection (n=179; 22.8%). Causes related to lack of information (n=16; 2.0%) or other patient-related causes (n=21, 2.7%) were rare (Table 29).

The most common drug classes involved in DRPs were drugs affecting the nervous system (ATC class N, 28% of drugs, n=236) and cardiovascular drugs (ATC class C, 21%, n=178). The most frequently reported drug groups were antidepressants, and hypnotics and sedatives (Table 30). Three individual drugs: calcium supplement (n=39), furosemide (n=32) and paracetamol (n=27), each caused DRPs in more than 20% of the patients (Table 30), as did opioid analgesics (n=37).

Of the 785 DRPs, 83% (n=649) resulted in intervention recommendation to the physician from the pharmacist (Table 31). Physicians accepted 55% (n=360) of the recommendations as made. As a result of the case conference, interventions at the drug-level were agreed to in 51% (n=403) of DRPs (Table 31). Of these interventions, most common was to stop the drug (32% of the drug-level interventions, n=128) or to change drug dose (23%, n=93). Drug-level interventions related to analgesics were agreed to often and included e.g., discontinuation of non-steroidal anti-inflammatory drugs (NSAIDs), changing doses of paracetamol and changing opioids to other analgesics (Table 32).

Table 28. *Most common DRPs (n=785) and the associated drug groups in CMR patients aged 65 and older (n=121)*

Drug-related problem	Home-dwelling patients (n=70)		Assisted-living patients (n=51)		p[a]	Three drug groups most commonly involved in the DRPs listed (n)
	%	n	%	n		
P2.1. Inappropriate drug	16.2	82	19.3	54	NS	Hypnotics and sedatives (16), anxiolytics (14), meprobamate (9)
P2.6. No drug prescribed but clear indication	15.4	78	16.8	47	NS	Calcium[b] (14), statins (12), ACE inhibitors (9)
P3.2. Drug dose too high or dosage regimen too frequent	11.9	60	12.5	35	NS	Drugs for ulcer (16), furosemide (13), hypnotics and sedatives (10)
P1.1. Side-effect suffered (non-allergic)	10.1	51	11.8	33	NS	Opioid analgesics (9), ACE inhibitors (8), furosemide (7)
P3.1. Drug dose too low or dosage regimen not frequent enough	10.1	51	6.8	19	NS	Paracetamol (12), calcium[b] (9), adrenergic inhalants[c] (6)
P5.1. Potential interaction	6.5	33	6.1	17	NS	Antidepressants (11), warfarin (10), iron (8)
P2.5. No clear indication for drug use	5.7	29	6.4	18	NS	Antidepressants (6), drugs for ulcer (3), antipsychotics (3)
Other DRPs	24.0	121	20.4	57		
Total	100.0	505	100.0	280		Antidepressants (52), hypnotics and sedatives (47), calcium[b] (39)

[a] Pearson Chi-Square test
[b] Includes calcium supplements with vitamin D
[c] Includes combination products with glucocorticoids
NS=not significant

Table 29. *Causes for DRPs (n=785) in CMR patients aged 65 and older (n=121)*

Cause	%	n
C1. Drug/Dose selection	**79.4**	**623**
C1.1. Inappropriate drug selection	22.8	179
C1.2. Inappropriate dosage selection	14.3	112
C1.3. More cost-effective drug available	0	0
C1.4. Pharmacokinetic problems, incl. ageing, interactions	14.1	111
C1.5. Synergistic/preventive drug needed and not given	11.5	90
C1.6. Deterioration/improvement of disease state	3.6	28
C1.7. New symptom or indication revealed/presented	3.3	26
C1.8. Manifest side effect, no other cause	4.7	37
C1.9.Treatment not discontinued/intervalled appropriately[a]	5.1	40
C2. Drug use process	**11.3**	**89**
C2.1. Inappropriate timing of administration and/or dosing intervals	4.7	37
C2.2. Drug underused/under-administered	2.7	21
C2.3. Drug overused/over-administered	0.9	7
C2.4. Therapeutic drug level not monitored	0.8	6
C2.5. Drug abused (unregulated overuse)	0	0
C2.6. Patient unable to use drug/form as directed	2.3	18
C3. Information	**2.0**	**16**
C3.1. Instructions for use/taking not known	1.3	10
C3.2. Patient unaware of reason for drug treatment	0.6	5
C3.3. Patient has difficulties reading /understanding patient information form	0	0
C3.4. Patient unable to understand local language	0	0
C3.5. Lack of communication between healthcare professionals	0.1	1
C4. Patient/Psychological	**2.7**	**21**
C4.1. Patient forgets to use/take drug	0.4	3
C4.2. Patient has concerns with drugs	0.4	3
C4.3. Patient suspects side-effect	0	0
C4.4. Patient unwilling to carry financial costs	0.4	3
C4.5. Patient unwilling to bother physician	0.0	0
C4.6. Patient unwilling to change drugs	0.0	0
C4.7. Patient unwilling to adapt lifestyle	0.0	0
C4.8. Burden of therapy	0.1	1
C4.9. Treatment not in line with health beliefs	0.1	1
C4.10. Patient takes food that interacts with drugs	0.3	2
C4.11. Other patient-related cause[a]	1.0	8
C5. Logistics	**0.3**	**2**
C5.1. Prescribed drug not available (anymore)	0	0
C5.2. Prescribing error (only in case of slip of the pen)	0	0
C5.3. Dispensing error (wrong drug or dose dispensed)	0.3	2
C6. Other	**4.3**	**34**
C6.1. Other cause; specify	0.6	5
C6.2. No obvious cause	3.7	29

[a] DRP cause classes added to the PCNE Classification for DRPs version V5.01.

Table 30. *Ten therapeutic drug groups most commonly involved in DRPs (n=785) in CMR patients aged 65 and older (n=121)*

Drug group	%	n	Three DRPs most frequently related to the drugs (n)
Antidepressants	6.3	52	Potential interaction (11), drug dose too high (6), no clear indication (6)
Hypnotics and sedatives	5.7	47	Inappropriate drug (16), duration of treatment too long (11), drug dose too high (10)
Calcium supplement[a]	4.7	39	No drug but clear indication (14), drug dose too low (9), potential interaction (4)
Antithrombotic agents	4.7	39	Potential interaction (14), inappropriate drug (4), inappropriate duplication (4), drug dose too high (4)
Opioid analgesics	4.5	37	Side-effect suffered (9), inappropriate drug (8), potential interaction (5), inappropriate drug form (5)
Proton pump inhibitors	4.1	34	Drug dose too high (16), no drug but clear indication (4), no clear indication (3)
Loop diuretics (furosemide)	3.9	32	Drug dose too high (13), side-effect suffered (7), inappropriate drug (5)
Anxiolytics	3.6	30	Inappropriate drug (14), duration of treatment too long (5), side-effect suffered (3)
Other analgesics and antipyretics[b]	3.5	29	Drug dose too low (12), drug dose too high (4), patient dissatisfied with therapy (4)
Beta blocking agents	3.2	27	Side-effect suffered (5), inappropriate drug (5), no drug but clear indication (4), drug dose too low (4)
Sum	44.0	366	
Others	56.0	465	
Total	**100**	**831**	

[a] Includes combination products with vitamin D
[b] Includes paracetamol n=27
Note that a single problem (drug-drug interaction, duplication) may involve two drugs.

Table 31. *Interventions for DRPs (n=785) in CMR patients aged 65 and older (n=121)*

Intervention	% of DRPs	n
I1. At prescriber level	**100**	**785**
I1.1. Prescriber informed only	9.4	74
I1.2. Prescriber asked for information	7.9	62
I1.3. Intervention proposed, approved by prescriber	45.9	360
I1.4. Intervention proposed, not approved by prescriber	28.5	224
I1.5. Intervention proposed, outcome unknown	2.2	17
I1.6. Intervention proposed, carried out before case conference[a]	1.9	15
I1.7. Intervention proposed, prescriber carried out other intervention[a]	4.2	33
I2. At patient/carer level	**23.2**	**182**
I2.1. Patient (medication) counseling	21.9	172
I2.2. Written information provided only	0	0
I2.3. Patient referred to prescriber	0	0
I2.4. Spoken to family member/caregiver	1.3	10
I3. At drug level	**51.3**	**403**
I3.1. Drug changed	7.0	55
I3.2. Dosage changed	11.8	93
I3.3. Formulation changed	1.7	13
I3.4. Instructions for use changed	6.8	53
I3.5. Drug stopped	16.3	128
I3.6. New drug started	7.8	61
I4. Other intervention or activity	**9.4**	**74**
I4.1. Other intervention (specify)[b]	9.4	74
I4.2. Side effect reported to authorities	0	0

[a] Intervention classes added to the PCNE Classification for DRPs version V5.01.
[b] Other interventions included for example laboratory tests or dosing aids
Note, that only prescriber-level interventions were available for all DRPs.

Table 32. *Drugs most commonly involved in drug-level interventions (n=403) in CMR patients aged 65 and older (n=121)*

Drug-level intervention	%	n	Three drug groups most commonly involved in the interventions listed (n)
I3.1. Drug changed	13.6	55	Opioid analgesics (6), antidepressants (5), hypnotics and sedatives (5)
I3.2. Dosage changed	23.1	93	Paracetamol (11), drugs for peptic ulcer (11), furosemide (8)
I3.3. Formulation changed	3.2	13	Calcium supplement[a] (2), antidepressants (2), several single drugs (1)
I3.4. Instructions for use changed	13.2	53	Organic nitrates (7), hypnotics and sedatives (4), calcium[a] (4), iron (4), anxiolytics (4)
I3.5. Drug stopped	31.8	128	Hypnotics and sedatives (14), NSAIDs (9), antidepressants (8)
I3.6. New drug started	15.1	61	Calcium supplement[a] (9), lubricant eye drops (6), ACE inhibitors (5)
Total	**100**	**403**	

NSAIDs=non-steroidal anti-inflammatory drugs
[a] Includes combination products with vitamin D

8 Discussion

8.1 Appropriateness of Pharmacotherapy Among Home-Dwelling Aged (I, IV)

Based on this study approximately 15% of the entire Finnish outpatient population aged 65 or older used potentially inappropriate drugs according to the Beers criteria (Fick et al. 2003) in 2007 (I). Compared to most international studies (Tables 13–15) the percentage is low. The main cause for the fairly low prevalence, especially compared to studies from the USA (Table 13), is probably the limited number of PIMs available in Finland, as is the case in most other European countries (Fialova et al. 2005). At the time of this study only 37 of the 78 individual drugs listed in the Beers 2003 criteria (Fick et al. 2003) were available as oral medications in Finland. Since then 4 additional PIMs have been removed from the market in Finland. Thus, the authorities responsible for licensing drugs may have great influence on PIM prescribing. Also, there is a need for both national modifications and regular updating of PIM criteria to take into account changes and national differences in drug compendia (Dimitrow et al. 2011).

During CMR among outpatients aged ≥65 years, a choice of inappropriate drug (i.e., not most appropriate for indication) was the most commonly reported DRP (IV). Of the drugs involved in this DRP the most common were hypnotics, sedatives, anxiolytics and meprobamate (Table 28), i.e., similar drugs that are listed in the Beers criteria (Fick et al. 2003). Still it must be acknowledged that the Beers criteria is just one tool that the pharmacists use during the CMR to evaluate the appropriateness of pharmacotherapy (III). In CMR inappropriateness has a broader meaning and may be related to e.g., choice of ineffective drug, inappropriate drug-drug or drug-disease combinations, or unsuitability due to impaired kidney function or according to care guidelines (Figure 13). Thus, several sources of information should be utilized to address inappropriate use in addition to the Beers criteria (www.kaypahoito.fi, Socialstyrelsen 2003, 2010, Kivelä and Räihä 2007, Lääkeinteraktiot SFINX 2011, Renbase 2011). Furthermore, individual clinical evaluation should be the basis for all recommendations during CMR.

8.1.1 Benzodiazepines (I, IV)

The common use of benzodiazepines and especially the prominent high-dose temazepam prescribing in Finland (I) is a worrying and a more distinctive finding compared to most studies that have assessed PIM use in other countries (Tables 13–15). In Finland, the high use of benzodiazepines and other psychotropic drugs among the aged has been evident in numerous earlier studies (Linjakumpu et al. 2002b, Pitkälä et al. 2002b, Hartikainen et al. 2003a,b, Hartikainen and Klaukka 2004, Hosia-Randell et al. 2008) and recognized as a significant concern by the Ministry of Social Affairs and Health (2006). Compared to the earlier Finnish studies this one provides a national perspective, but it is important to note

that the results underestimate the use of benzodiazepines by excluding the benzodiazepines that are not included in the Beers criteria (Fick et al. 2003) or could not be analysed by using the SII data, i.e., non-reimbursable products or packages and certain dose- and duration dependent PIMs.

The negative outcomes associated with benzodiazepine use among older people are well documented. These include e.g., increased risk for falls and fractures (Ensrud et al. 2002, Wagner et al. 2004, Landi et al. 2005), impaired cognitive function (Barker et al. 2004), decline in physical performance and increased risk for urinary incontinence – a common cause for institutionalization (Landi et al. 2002, Gray et al. 2003). In addition to the harm to individual patients, the benzodiazepine-related ADEs may result in a significant economical burden for the health care system. In the European Union the estimated total hospital costs of benzodiazepine-related fall injuries alone were 1.5–2.2 billion euros in 2000, of which 90% occurred among elderly patients (Panneman et al. 2003). Regarding costs associated with all PIMs, in the USA their use was estimated to cause incremental healthcare costs of USD 7.2 billion in 2001 (Fu et al. 2007). Thus, actions targeted in reduction of benzodiazepine and other PIM prescribing for elderly patients seem reasonable.

A large part of the prescribing of benzodiazepines for elderly outpatients is likely to be for insomnia and other sleep disorders (Ohayon et al. 1998). A meta-analysis on the risks and benefits of sedative hypnotics in older people with insomnia indicated that the benefits are marginal and outweighed by the risks (Glass et al. 2005). Behavioral treatment methods of insomnia are effective and should be given preference among the aged because of the various potential adverse effects of benzodiazepines and benzodiazepine receptor agonists (Bloom et al. 2009).

If prescribing a benzodiazepine is still considered necessary, the national recommendations in Finland indicate temazepam as the preferred treatment among the aged (Kivelä and Räihä 2007). This is the probable explanation for its high prevalence of use in the current (I) and earlier Finnish studies (Raivio et al. 2006, Hosia-Randell et al. 2008). For temazepam the maximum recommended dose for elderly patients is only 10 mg (Kivelä and Räihä 2007). According to the current and previous studies, this dose-recommendation is not followed well in Finland (Raivio et al. 2006, Hosia-Randell et al. 2008). In addition to the recommendation of small doses, benzodiazepine treatment for insomnia should be short term and intermittent (Kivelä and Räihä 2007). In this study small package sizes, potentially prescribed for occasional or short-term use, were excluded from the analysis, because they are not reimbursed by the SII. Thus, the results of this study are likely to reflect regular or long-term use of benzodiazepines, and indicate that the recommendation of short-term treatment is not followed well either. The results of the study among CMR patients (IV) are consistent with the above mentioned conclusions. Hypnotics, sedatives and anxiolytics, i.e., ATC classes including mostly benzodiazepines, caused nearly 10% of all DRPs (Table 30). The most common DRPs with these drugs were, in addition to inappropriate drug choice, too high dose and too long duration of treatment.

Withdrawal of long-term benzodiazepine treatment should be accomplished by involving the patient and undertaking in a process of tapering use of the drug with an

individual schedule from 4 weeks to several years (Lader et al. 2009). For a primary care physician discontinuation of an elderly patient's benzodiazepine treatment may be challenging even if the potentially harmful long-term use of it is recognized. This is especially true if the physician sees the patient rarely and the prescriptions are repeated without a face-to-face contact with the prescriber, which is not exceptional in Finland (Saastamoinen et al. 2008). In international studies medication reviews involving pharmacists have been found to reduce suboptimal prescribing and to reduce psychotropic drug prescribing (Chrischilles et al. 2004, Nishtala et al. 2008, Castelino et al. 2009). In this study (IV) stopping of hypnotics and sedatives was the most commonly agreed drug-level intervention resulting from CMR. Because pharmacists visited patients at home, it is possible that they informed the collaborating physicians about psychotropic drug use that the physicians were not previously aware of. On the other hand, when physicians referred patients to the CMR, they may already have recognized the potentially harmful psychotropic drug use. As a result of the collaborative CMR procedure where the physician has the support of nursing staff and the pharmacist in the realization of long-term drug changes and follow-up, intervening with the problem may be easier. For this reason it is critical, that e.g., the home health care nursing personnel participate in the CMR case conference or are otherwise effectively informed about the decisions because they are in a key position to implement the drug changes.

The results of this study do not reveal whether the actions agreed during CMR case conferences were actually implemented or if the changes in drug regimen were sustained over time. Further studies are needed to identify effective and practical ways to implement medication changes during CMR. Particularly, it is important to ascertain that the patients are properly informed about the changes and their reasons in order to engage them in following the new drug regimen. Otherwise it is possible that the changes will not be sustained or discontinued drugs may be substituted by others (Pitkälä et al. 2001).

8.1.2 Anticholinergic Drugs (I, III, IV)

Anticholinergic drugs may cause several ADEs that are more frequent among the aged, e.g., falls, dry mouth, dry eyes, constipation, dizziness, confusion, delirium and impaired cognitive function (Rudolph et al. 2008, Campbell et al. 2009). Of the anticholinergic drugs listed in the Beers criteria (Fick et al. 2003), the tricyclic antidepressant amitriptyline was used by 2% of the elderly outpatient population in this study (I). The common use of amitriptyline is consistent with numerous international studies (Tables 13–15). There are some indications where amitriptyline may be useful in elderly care (Zhan et al. 2001). In Finland, it is commonly used to treat neuropathic pain, for which purpose it has the best evidence and is available at an affordable price (Attal et al. 2010). Among elderly patients amitriptyline could be replaced with desipramine, nortriptyline, venlafaxine, duloxetine or pregabalin, all of which have more favourable adverse effect profiles (Davis and Srivastava 2003, Barber and Gibson 2009, Attal et al. 2010). However, desipramine is not on the market in Finland and nortriptyline is not officially indicated for pain, which prevents Finnish physicians from following the international

recommendations in relation to use of these agents for this purpose (Davis and Srivastava 2003, Barber and Gibson 2009).

During the CMR accreditation training, pharmacists learn about the potential adverse effects of anticholinergic drugs among elderly patients. In addition, questions regarding anticholinergic ADRs are included in the CMR interview to highlight their importance (III; Appendix 2). Never the less tricyclic antidepressants (TCAs) or other anticholinergic drugs were not prominently evident in DRPs during CMRs in this study (IV). This may partly be due to the study method, which grouped TCAs under the same ATC group with other antidepressants. However, in a more detailed analysis of the same CMR data, 13 persons were using amitriptyline or doxepine, but after CMR these medicines were stopped only for three patients (Dimitrow 2009). Instead, need for regular use of these agents was emphasized for four patients and added as a new treatment for two more in order to improve management of chronic pain. This indicates that the individual properties and needs of the patients are more important in CMR than general recommendations with regard to avoidable drugs. As a consequence, each patient's medications need to be reviewed against their personal clinical data during CMR before any recommendations can be made for changing their treatment.

8.1.3 Undertreatment (III, IV)

Simple application of PIM criteria to a patient population addresses a narrow part of the appropriateness of pharmacotherapy and does not consider individual patient characteristics. CMR is designed especially to take into account the individual needs of the patient with regard to all important dimensions of appropriate pharmacotherapy, including undertreatment, treatment outcomes and factors that may influence adherence (III). In this study (IV) the patients used a very high mean number of drugs (12.3 regular prescription drugs/person). Still, the second most common DRP reported by pharmacists was, somewhat surprisingly, an indication with no treatment (IV). Undertreatment was related most often to prevention or treatment of cardiovascular diseases and osteoporosis. This finding is consistent with several earlier studies (Strandberg et al. 2003, Gaw 2004, Higashi et al. 2004, Sloane et al. 2004, Barry et al. 2007, Rao et al. 2007, Ramalho de Oliveira et al. 2010). As a result of CMR, calcium supplements for prevention or treatment of osteoporosis were started often but for example statins for hypercholesterolemia not (Table 32). This again points out the importance of individualized decisions during CMR; the pharmacist can make recommendations based on patient's conditions, test results and current care guidelines (www.kaypahoito.fi) but the physician must judge whether preventive therapies, such as statins, are likely to benefit the individual patient.

Undertreatment or poor control of pain among Finnish home-dwelling older people has been shown in earlier studies (Pitkälä et al. 2002a, Hartikainen et al. 2005). In CMR procedure, the patient interview includes questions related to pain and also ADRs that may be caused by analgesics, e.g., constipation resulting from opioid use (III; Appendix 2). Treatment of pain seemed to have room for improvement among elderly CMR patients, since underdosing of paracetamol and DRPs involving opioid analgesics were common

(IV; Table 30). Opioids increase the risk for fractures and cognitive impairment and the adverse gastrointestinal, cardiovascular and renal effects of non-steroidal anti-inflammatory drugs (NSAIDs) are well established, so it is particularly important to assure their rational use (Griffin et al. 1991, Vestergaard et al. 2006, Wright et al. 2009, American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons 2009). In this study several changes that comply with care recommendations were made on pain medications as a result of CMR, e.g., discontinuation of NSAIDs, increasing doses of paracetamol and changing opioids for other alternatives (Table 32). In the future, studies to evaluate the impact of CMR on pain and health-related quality of life are needed.

8.2 CMR Accreditation Training (II)

The new collaborative clinical role of the pharmacists during CMR requires skills and knowledge that are currently more or less lacking in their education in Finland. These include, e.g., collaboration with other health care professionals, selection of evidence-based pharmacotherapy, interpretation of laboratory test results, knowledge on special features of geriatric pharmacotherapy and developing individualized drug treatment plans. The CMR accreditation training was developed to meet these competency needs. According to this study the participating pharmacists' satisfaction with the training was high and the training met their educational needs. A majority of the course participants believed they would continue to conduct CMRs after the training and none of the participants mentioned lack of skills as a barrier for future CMRs. This suggests that the goals of the training were achieved.

This study was performed in the early phase of starting the CMR service implementation in Finland. Since then 1–2 CMR accreditation training courses have been organized annually with about 40–50 pharmacists from hospital and community pharmacies participating. Surveys to measure participant responsiveness to the training have been conducted after every course. Participant satisfaction with the training has continued to be high. Contents of subsequent courses are always planned based on the feedback from the previous ones. So far, there has been no need to make major changes to the curriculum. If more clinical pharmacy and collaborative skills are taught in the basic training of pharmacists in the future, this may also affect the contents of the CMR accreditation training.

8.3 CMR Procedure and Outcomes (II, III, IV)

8.3.1 CMR Procedure (II, III)

Internationally, there are numerous different medication review procedures which differ in their comprehensiveness, pharmacists' access to patient data and patient involvement (Chapter 2.2). Published literature generally lacks information how these procedures have been developed, what is the evidence behind their actions, and what measures are used in the procedures and why. Also, in published studies the medication review procedures are often poorly and inadequately described even if the interventions are likely to affect the outcomes of such studies (Holland et al. 2005, Smith et al. 2006). The development process of CMR is unique in its extensiveness; it involved a strong component of literature-based development to find evidence for the actions and measures of the procedure but also remarkable practical development and testing to make the procedure applicable to the Finnish health care system.

A crucial idea in CMR was to develop a service that is carried out in a uniform manner by each reviewer, so that the patients and the payers of the service can count on a high standard of quality (see Stubbings et al. 2011). This is first accomplished by the CMR accreditation training (II) that ascertains that all accredited pharmacists are competent to conduct the reviews. A basic requirement to be accepted to the CMR training course; the Bachelor's or Master's degree in Pharmacy, was to guarantee sufficient skills in pharmacology and pharmacotherapy. This allows the training to focus on supplementing existing knowledge with more detailed information on geriatric pharmacotherapy. Secondly, the CMR procedure follows a standard structure that has undergone extensive evidence- and practice-based development and testing to meet the needs of the patients and collaborating health care professionals and to be compatible with the Finnish health care system (III). Finally, the CMR documentation, if used properly, is a guarantee of uniform quality as it systematically guides every step of the CMR procedure. This is especially important during the patient interview, so that all necessary information for the medication review can be gathered, and at the time of the actual medication review and reporting of the findings to the collaborating physician.

Due to its focus on standard quality goals and comprehensiveness, especially with regard to the home-visit, the CMR procedure is laborious and takes at least several hours. In spite of the time required to do it, the CMR accreditation training participants in this study (III) saw the patient interview as a crucial part of the CMR procedure. The training participants saw this as necessary to provide information to promote rational drug use and adherence and to attain relevant information that was not available in patient records or known by the attending physician. Also, the pharmacists participating in the training did not want to remove any questions from the extensive interview form. Instead, new questions were added based on their suggestions. Indeed, the added questions, e.g., regarding health habits are very important when medications are reviewed. For instance, smoking and alcohol may have clinically significant interactions with drugs and such issues may not have been discussed with the caretaking physician (Weathermon and Crabb

1999, Kroon 2007). Delicate issues, such as alcohol consumption, are easier to bring up to discussion, if they are part of a standard procedure.

Internationally the benefits of in-home interviews are well documented, and include recognition of problems in drug administration that are otherwise difficult to detect, e.g., hoarding, inappropriate storage conditions, expired medications or confusion between generic and brand names (Hsia Der et al. 1997, Frank et al. 2001, Sorensen et al. 2006). It is also known that discrepancies between the medication lists of physicians and actual drug use are common, and may result in drug interactions and ADEs (Frank et al. 2001, Tulner et al. 2008). In-home visits have been shown to produce the most reliable medication lists (Yang et al. 2001). In the future electronic health records may help to attain reliable prescription drug lists (Westerling 2011), but do not provide information on OTC drugs, herbal products and actual use of drugs. It could be possible that multiprofessional collaboration, e.g., home health care nurses could be utilized more efficiently in CMR to acquire the data on actual drug use. On the other hand, they lack the skills of pharmacists in providing medication counseling at home, which also is an important component of CMR.

The CMR clearly expands the Finnish community and hospital pharmacists' role in the health care compared to the traditional tasks, which have mainly consisted of preparing and dispensing of drugs and patient counseling. Importantly, in CMR the pharmacists have access to clinical patient data, including diagnoses and laboratory test results and can discuss, e.g., individualized treatment goals with the physician. This is a clear distinction from traditional counseling during which the pharmacists base their advice on the often insufficient or unreliable information available on the prescription or provided by the patient.

Access to extensive clinical patient data is crucial for the pharmacists to undertake reliable analysis of the patient's pharmacotherapy and make valid recommendations for the collaborating physician during CMR. Still, there is currently no efficient way to transfer patient data from physician to pharmacist. The CMR Referral and Data Transfer Form developed for this purpose in this study was judged by the study pharmacists as being too laborious for the collaborating physician (III). This may prevent the physicians from making the referrals and also gaining the intended benefit of CMR as a practical, time-saving decision-making support tool. Prints of patient medical records, a way preferred by several pharmacists in this study, may, on the other hand, be an impractical and time-consuming way for the pharmacist to gather relevant data. In the future more effective and reliable ways for this data transfer will need to be developed (see also Westerling 2011). This also applies to transfer of information after CMR case conference to all persons that are involved in patient's medical care and following-up his/her condition at home. Electronic health records and community pharmacists' access to them or other protected electronic data transfer system would make the CMR process more feasible (Westerling et al. 2011, Westerling 2011).

8.3.2 Outcomes of CMR Compared to MTM and HMR (IV)

In this study (IV) the pharmacists were able to recognize a large number of DRPs among the elderly outpatients. They reported an average of 6.5 DRPs per person to the collaborating physicians. Because the DRPs that were resolved at the patient's home by the pharmacist were probably not reported to physicians, this result is likely to underestimate the number of actual DRPs. Still, the number of DRPs was high compared to MTM studies from the USA (1–3.6 DRPs/encounter; Table 10). There are several potential explanations for this. First, in MTM, patient encounters usually take place at the pharmacy or even by phone, and may last for as little as five minutes (Ellis et al. 2000b). The more thorough discussions and comprehensiveness of the review in Finland may be the cause of significantly higher mean number of DRPs reported by the pharmacists in this study. Secondly, in MTM there are usually several follow-up encounters. Thus, the pharmacist is not compelled to report all findings at once, which means that the number of DRPs per encounter may be smaller. Also in the Australian HMR studies the mean number of DRPs/patient (2.1–9.7; Table 11) has been generally lower than in this study, even though the procedure involving a home visit seems to be similar to CMR. As HMR and MTM are not solely targeted at elderly patients, part of the lower number of DRPs may relate to the younger mean age of patients and lower number of used drugs in most reviewed studies (Tables 10, 11).

The older patient population in this study may also explain the difference in the most common DRP types found in this study compared to those found in MTM and HMR studies (Tables 10, 11). In this study "inappropriate drug choice", involving especially hypnotics and sedatives, was the most commonly reported DRP (IV). This different finding compared to MTM and HMR is understandable, because the specific risks of psychotropic drugs, e.g., falls and fractures, are pronounced among elderly patients and the criteria and recommendations to indicate inappropriate drugs only apply to people aged 65 or 75 and older who were not solely represented in most HMR and MTM studies (Chapters 3.2.1, 3.2.2). On the other hand, DRPs related to poor adherence and patients' lack of knowledge were common in the majority of MTM and HMR studies. In this study such patient-related DRPs or causes of DRPs were rare. This may either indicate that CMR focused more on clinical findings or that the study method prevented recognition of adherence-related DRPs that were solved by the pharmacist at the patient's home.

Even though MTM and HMR were used as models when the CMR procedure was developed, the above mentioned differences in the medication review models, pharmacists findings and patient populations, make it unreliable to draw any direct comparisons between the potential outcomes of CMR and those based on MTM and HMR studies (Tables 4, 5).

8.3.3 CMR in the Finnish Health Care System (II, III, IV)

After completing the CMR accreditation training, about one third of the accredited pharmacists were still uncertain whether they would conduct CMRs in the future (II), even

if they knew that keeping up both practical and theoretical competencies is required for reaccreditation. Several mentioned that the development of a local CMR service was difficult and time-consuming. Indeed, Finnish hospital and community pharmacists have not traditionally been expected to be involved in patient care. In addition, they are not used to develop professional services based on their special expertise. Also, they are not used to actively promote this kind of expert services and make contracts with public or private purchasers (see also Stubbings et al. 2011). As a result, in recent CMR accreditation training courses the assignment to establish a CMR service has been rescheduled to start in an earlier phase of the training to facilitate development of a permanent CMR collaboration. The TIPPA Coordination Group intends to conduct a survey among all approximately 150 pharmacists accredited to conduct CMRs to see how the CMR practice is evolving in Finland and how many of those accredited stay active in conducting CMRs.

The greatest challenge for CMR in Finland is that there are no national systems in place to integrate CMRs in the health care, including lack of specific eligibility criteria and guidelines for reimbursement of CMR. During the development phase of CMR the pharmacists tested various CMR procedures in collaboration with their health care partners in order to develop a model that the partners find useful and that could fit in the Finnish health care system (III). Some pharmacies with accredited pharmacists have succeeded to make contracts with municipalities and agree on payment and other conditions. Such contracts are not common even though already in 2007 the Ministry of Social Affairs and Health recommended that the municipalities should assure that the medications of the elderly residents are reviewed annually even if no changes were made in their regimen. Collaborative medication reviews were recommended as a way of conducting the medication reviews and community pharmacists were urged to charge for the medication reviews on an hourly basis (Ministry of Social Affairs and Health 2007).

The current patient selection criteria for CMR is broad and varies locally. There is no national, evidence-based standard criteria, but the pharmacists, collaborating physicians and nurses agree on applicable patients. In this study a mean of 3 drug changes per patient were agreed on during the CMR case conference (IV). The high number of drug changes indicates that there is room for improvement in the patients' pharmacotherapy and that the patient selection was successful. However, the intentional selection of elderly, high-risk patients with potential problems in their pharmacotherapy for this study makes the results non-generalizable to all elderly patients. On the other hand, this kind of time-consuming expert service should be targeted to those patients who have some special potential problems in their medication use, and thus, can benefit from the service.

In the future it is important to study which patients are likely to gain the best benefit from CMR and to develop more specific guidance regarding suitable eligibility criteria. Currently, a risk assessment tool to identify potential risk patients among home health care patients is being pilot tested (Salminen 2011). Such tool may be useful in development of eligibility criteria and in advancing the use of CMR in the health care system.

8.4 Future Studies

There are several issues that may have influenced the prescribing of PIMs since 2007, when this study (I) was conducted. Firstly, the Finnish Medicines Agency published its criteria to indicate potentially inappropriate drugs for people aged 75 and older in 2010 (Fimea 2011). As an open-access database it can be widely used by health care professionals and affect prescribing practices. Secondly, there are changes in drug compendium that may affect PIM prescribing, e.g., removal of drugs from the market. In addition, in 2007 the Ministry of Social Affairs and Health pointed out the potential problems in elderly care in Finland and gave national recommendations for actions for municipalities responsible for organizing healthcare for their residents. One of the recommended actions was annual medication reviews for all aged residents (75 years or older). It would be interesting to conduct a national follow-up study to evaluate whether these recommended actions have been acted on and have had any impact on medication use of elderly. As part of such study, it would be necessary to assess the implementation rate of actions and possible regional variation in quality of care. Regarding CMR, sound evidence is still missing on its clinical, humanistic and economic outcomes. The same applies to other medication reviews procedures applied in other countries (Lipsanen 2009).

The current study was conducted at the time when CMR procedure was under development and the collaboration between pharmacists and physicians was just starting to evolve in Finland. Now, there is need for studies that would assess the effects of CMR on health outcomes, including clinical outcomes, HRQoL, and health care costs. The outcomes of HMR and MTM studies (Tables 4, 5) can provide limited insight with regard to the potential benefits, but as most related studies are not targeted to elderly patients, their results are not directly applicable to CMR. Also, the differences in the procedures, e.g., lack of home visit in MTM, and the specific competences of CMR pharmacists gained during the long-term accreditation training may affect the results. The Finnish Medicines Agency Fimea has shown interest in CMR and is currently planning a research project to evaluate the effects of CMR, possibly compared to some less comprehensive medication review model. The results of such studies may greatly affect policymaking and demand for CMR services in Finland. It would be useful if such studies could indicate which patients are likely to benefit from an in-depth review procedure like CMR and if less resource-intensive medication review models are useful, perhaps as a routine practice, for others.

9 Conclusions

Approximately 15% of the entire Finnish outpatient population aged 65 and older use potentially inappropriate drugs. One third of this drug use involves benzodiazepines, particularly high-dose temazepam. Compared to international studies the prevalence of PIM use in Finland is low. However, the common use of benzodiazepines is a worrisome finding, as they increase the risk for falls and fractures and are associated with impaired cognitive function.

The CMR accreditation training and CMR procedure are developed to increase pharmacists' involvement in assuring rational and safe pharmacotherapy. The CMR training provides the hospital and community pharmacists with sufficient knowledge and skills to conduct CMR in collaboration with other health care professionals, particularly with physicians. The pharmacists' satisfaction with the training is high, but several factors inhibit pharmacist from conducting CMRs after the training.

The CMR procedure is based on a detailed development process. The development involved a literature review, inventory of international medication review procedures, development of potential procedures by CMR accreditation training participants, integration of potential procedures to a national standard procedure and piloting in practice setting. The resulting collaborative CMR procedure includes access to clinical patient information, a patient home interview and a case conference with the physician. The CMR procedure covers four relevant dimensions of ascertaining rational and safe pharmacotherapy among elderly patients: Aging and Safety; Co-Morbidities; Polypharmacy; and Adherence. Extensive CMR documentation is developed to support the procedure and guarantee uniform quality of CMRs.

By using the CMR procedure, pharmacists are able to recognize DRPs. Among outpatients aged 65 and older, an average of 6.5 DRPs per patient were reported to physicians during CMR. Most common DRPs were inappropriate drug selection, especially involving psychotropic drugs, and undertreatment of cardiovascular diseases and osteoporosis. Also treatment of pain was often found to need improvement. Approximately half of the pharmacists' recommendations led to medication changes and an average of 3 changes to drug regimen were made per patient. Positively, most common agreed change was to stop hypnotics or sedatives.

The results of this study confirm many well-known problems in elderly pharmacotherapy: prescribing of inappropriate drugs, undertreatment, and issues related to inadequate management of pain. The CMR procedure could be beneficial for improving pharmacotherapy among older outpatients as a large portion of identified problems lead to medication changes. Actions to facilitate implementation of the model to Finnish health care system are needed. Also, further studies are needed to evaluate the effects of CMR on clinical, humanistic and economic outcomes.

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Appendices

Appendix 1. Pharmaceutical Care Network Europe (PCNE) Classification scheme for drug-related problems V6.2 (www.pcne.org)

The Problems

Primary Domain	Code V6.2	Problem
1.Treatment effectiveness There is a (potential) problem with the (lack of) effect of the pharmacotherapy	**P1.1** **P1.2** **P1.3** **P1.4**	No effect of drug treatment/ therapy failure Effect of drug treatment not optimal Wrong effect of drug treatment Untreated indication
2. Adverse reactions Patient suffers, or will possibly suffer, from an adverse drug event	**P2.1** **P2.2** **P2.3**	Adverse drug event (non-allergic) Adverse drug event (allergic) Toxic adverse drug-event
3. Treatment costs The drug treatment is more expensive than necessary	**P3.1** **P3.2**	Drug treatment more costly than necessary Unnecessary drug-treatment
4. Others	**P4.1** **P4.2**	Patient dissatisfied with therapy despite optimal clinical and economic treatment outcomes *Unclear problem/complaint. Further clarification necessary (please use as escape only)*

- ☐ Potential Problem
- ☐ Manifest Problem

Appendix 1. Continued.

The Causes

Primary Domain	Code V6.2	Cause
1. Drug selection The cause of the DRP is related to the selection of the drug	**C1.1** **C1.2** **C1.3** **C1.4** **C1.5** **C1.6** **C1.7** **C1.8** **C1.9**	Inappropriate drug (incl. contra-indicated) No indication for drug Inappropriate combination of drugs, or drugs and food Inappropriate duplication of therapeutic group or active ingredient Indication for drug-treatment not noticed Too many drugs prescribed for indication More cost-effective drug available Synergistic/preventive drug required and not given New indication for drug treatment presented
2. Drug form The cause of the DRP is related to the selection of the drug form	**C2.1**	Inappropriate drug form
3. Dose selection The cause of the DRP is related to the selection of the dosage schedule	**C3.1** **C3.2** **C3.3** **C3.4** **C3.5** **C3.6** **C3.7**	Drug dose too low Drug dose too high Dosage regimen not frequent enough Dosage regimen too frequent No therapeutic drug monitoring Pharmacokinetic problem requiring dose adjustment Deterioration/improvement of disease state requiring dose adjustment
4. Treatment duration The cause of the DRP is related to the duration of therapy	**C4.1** **C4.2**	Duration of treatment too short Duration of treatment too long
5. Drug use process The cause of the DRP can be related to the way the patient uses the drug, in spite of proper dosage instructions (on the label)	**C5.1** **C5.2** **C5.3** **C5.4** **C5.5** **C5.6** **C5.7**	Inappropriate timing of administration and/or dosing intervals Drug underused/ under-administered (deliberately) Drug overused/ over-administered (deliberately) Drug not taken/administered at all Wrong drug taken/administered Drug abused (unregulated overuse) Patient unable to use drug/form as directed
6. Logistics The cause of the DRP can be related to the logistics of the prescribing and dispensing process	**C6.1** **C6.2** **C6.3**	Prescribed drug not available Prescribing error (necessary information missing) Dispensing error (wrong drug or dose dispensed)
7. Patient The cause of the DRP can be related to the personality or behaviour of the patient.	**C7.1** **C7.2** **C7.3** **C7.4**	Patient forgets to use/take drug Patient uses unnecessary drug Patient takes food that interacts Patient stored drug inappropriately
8. Other	**C8.1** **C8.2**	Other cause; specify No obvious cause

Appendix 1. Continued.

The Interventions

Primary Domain	Code V6.2	Intervention
No intervention	**I0.0**	No Intervention
1. At prescriber level	**I1.1**	Prescriber informed only
	I1.2	Prescriber asked for information
	I1.3	Intervention proposed, **approved** by Prescriber
	I1.4	Intervention proposed, **not approved** by Prescriber
	I1.5	Intervention proposed, outcome unknown
2. At patient/carer level	**I2.1**	Patient (medication) counselling
	I2.2	Written information provided only
	I2.3	Patient referred to prescriber
	I2.4	Spoken to family member/caregiver
3. At drug level	**I3.1**	Drug changed to…
	I3.2	Dosage changed to…
	I3.3	Formulation changed to…
	I3.4	Instructions for use changed to …..
	I3.5	Drug stopped
	I3.6	New drug started
4. Other intervention or activity	**I4.1**	Other intervention (specify)
	I4.2	Side effect reported to authorities

The Outcome of the Interventions

Primary Domain	Code V6.2	Outcome of intervention
0. Not known	**O0.0**	Outcome of intervention not known
1. Solved	**O1.0**	Problem totally solved
2. Partially solved	**O2.0**	Problem partially solved
3. Not solved	**O3.1**	Problem not solved, lack of cooperation of patient
	O3.2	Problem not solved, lack of cooperation of prescriber
	O3.3	Problem not solved, intervention not effective
	O3.4	No need or possibility to solve problem

Appendix 2. CMR Patient Interview Form. Questions marked with* were present already in the preliminary interview form.

COMPREHENSIVE MEDICATION REVIEW INTERVIEW FORM

Patient name: _____ Date _____
□ at home □ at the pharmacy □ at ward □ _____

The reason for this interview is to review the state of your current drug therapy. The answers you provide will be used to ascertain that your drug treatment is appropriate. The medication review will be discussed with your physician, who may change your drug regimen, if needed.
All received information will be kept confidential.

MEDICATION MANAGEMENT

*1. Which physicians have you visited during the past year (12 months)
□ Primary care physician
□ Specialist at hospital (e.g., internist, ophthalmologist)
□ Private sector physician (e.g., dermatologist, gynecologist)
□ Other, what? _____

2. Which physician is primarily responsible for your drug treatment?_____

3. Do you receive any help regarding medication management? Is dose dispensing used?
□ Managed self □ Home health care □ Relative _____ □ Other_____
□ Dose-dispensing devise □ Automated unit dose dispensing

USED PRESCRIPTION AND OTC DRUGS, NATURAL PRODUCTS AND DIETARY SUPPLEMENTS

*4. Please, let me see all prescription drugs you use. (The patient is asked to show all prescription drug products in use. The following issues are discussed regarding every product: storage conditions, patient's understanding of the purpose, actually used dose and dosing interval, is use only as needed, are there any difficulties regarding the drug. Drugs and doses are documented on a separate table, and compared to the medication list received from the collaborating physician.)

Dosing times: morning at ____, day at ____, afternoon at____, evening at ____, night at____

*5. Do you use any non-prescription drugs?
□ Yes □ No

*6. Please, let me see all non-prescription drugs you use. (Discussed and documented like prescription drugs. Additionally, it is asked who has recommended the use of the product.) As a reminder the pharmacist may bring up various drug groups for discussion:

□ Analgesics_____
□ Analgesic ointments_____
□ Other ointments _____
□ Drugs for allergy _____
□ Eye drops_____
□ Antacids, proton pump inhibitors _____
□ Laxatives_____
□ Cough medicines_____
□ Vitamins, minerals_____

*7. Do you use any natural products, dietary supplements or related products available e.g., in natural product shops or grocery shop?
□ Yes □ No

*8. Please, let me see all natural products etc. you use. (Discussed and documented like non-prescription drugs)

Appendix 2. Continued.

DRUG-RELATED PROBLEMS (DRPs)

*9. Do you have problems or difficulties with some drugs you use? What kind of problems? (The interviewer uses the table to describe examples of potential problems)

Problem	**Related drug/drugs**
The drug is not helping	
The drug seems to cause adverse effects	
Indication for use is not known	
Difficulties with administration: - Opening containers - Swallowing tablets/capsules - Using eye-drops - Using asthma inhaler - Insulin - Using the dose dispensing device	
Forgetting to take drugs	
Expensive drug/drugs	
Great number of drugs	
Other problems: □ Drugs with improper storage conditions found	

ADHERENCE

If nonadherence is the cause for CMR, Morisky adherence scale can be attached here.

*10. Do you currently use any drugs more or less than ordered by the physician?
□ Yes, more □ Yes, less □ All as instructed

*11. If you use any drugs more or less than prescribed, tell which drug/drugs and for what reason

Drug	Different dose / dosing frequency	Cause for different dosing (e.g., the drug does not help on prescribed dose)

*12. Have you discontinued a drug without telling your physician during the past 6 months (e.g., because of adverse effects or because the price was too high)
□ Yes □ No

*13. Which drug/drugs, when and for what reason?

_____

_____

*14. Would you like to have any changes made in your drug regimen? (The interviewer may describe examples, e.g., switch of tablet to liquid during swallowing difficulties.)
□ Yes □ No

*15. If yes, what kind of changes?

_____

_____

Appendix 2. Continued.

MONITORING

17. Do you self monitor e.g., blood pressure, blood glucose at home or does a visiting nurse etc. visit you to do the measurements?
□ No □ Yes, _____

Laboratory test results not included in preliminary patient data can be documented here:

Test	Result	Date	Goal	Note
Blood pressure			General goal <140/85 mmHg	Diabetics and other high-risk patients <130/80 mmHg
BG (fasting) BG (after meal)			4-6 < 8	
Hb1Ac			< 6-7	If no hypoglyceamias
Hb			>120 ♀ >130 ♂	
Chol LDL HDL Trigly			<5 <3 >1 <2	great risk (e.g., diabetes) <4.5 great risk <2,5 (if arterial events <1.8)
Krea GFR			♀: 50-90 ♂: 60-100 > 90	GRF= ♀: (140 – age) x weight / 0,95 x P-krea (µmol/l). ♂: (140 – age) x weight / 0,8 x P-krea (µmol/l).
Other				

□ Monitoring needed regarding:_____

ADVERSE EFFECTS, THEIR SEVERITY AND POSSIBLE TREATMENT

The next questions are about symptoms, that are common among elderly patients and may be associated with use of certain drugs. We want to know if you have experienced any such symptoms. Please, choose the alternative that best describes your situation during the past few days (weeks).

***DRYNESS OF MOUTH**[a] (due to decreased salivation)

Has a dry mouth troubled you?
□ Not at all
□ Slight dryness, not disturbing
□ Moderate and slightly disturbing dryness of mouth
□ Marked dryness of mouth which clearly disturbs daily life

If dryness of mouth has troubled you, how has it been treated?
□ Not treated □ Water/liquids □ Product: _____

Appendix 2. Continued.

***CONSTIPATION**[a] (reduced frequency of defaecation and/or thicker consistency of faeces)

Have you been troubled by constipation?
□ Not at all
□ Slight constipation, but bearable
□ More marked, hampering constipation
□ Very pronounced constipation (need to take laxatives)

If you have been troubled by constipation, how has it been treated?
□ Not treated □ Diet □ Product: _____

***MICTURITION DISTURBANCES**[a] (feeling of difficulty in starting and of resistance to micturition, weaker stream and/or longer time of micturition)

Have you experienced difficulties in passing your urine?
□ Not at all
□ Clearly present, but bearable (Difficulty in beginning urination)
□ Poor stream, takes longer to empty bladder, feeling of incomplete emptying of bladder
□ Cannot empty bladder, need help (retention of urine)

If you have experienced urinary disturbances, how have they been treated?
□ Not treated □ Reduced fluid intake □ Product: _____

DIZZINESS/FAINTING (orthostatic dizziness)[a]
(Dizziness can manifest as feeling of weakness, everything going black, buzzing in the ears or increasing tendency to faint when changing from supine or sitting position to upright position)

Does dizziness or fainting trouble you when getting up from a lying or sitting position?
□ Not at all
□ Sometimes, but I can stand up without problems
□ Must rise slowly from sitting or lying position
□ Difficulty in standing up due to dizziness of feeling faint

OTHER UPCOMING ADVERSE EFFECTS OR SYMPTOMS
□ Falls
□ Confusion
□ Others: _____

During medication review it is important to get information regarding your current health. The next questions address such issues.

PAIN

Have you suffered from pain during the last week?
□ Not at all
□ Mild or temporary pain
□ Moderate pain
□ Severe pain

If you have suffered from pain, how has it been treated?
□ Not treated □ OTC: _____□ Prescription: _____ □ Other: _____

Note! Pain figures are as an attachment. Can be used if appropriate.

Appendix 2. Continued.

INSOMNIA/SLEEPING DISORDERS (e.g., troubles falling asleep, night time awakenings)

Have you been troubled by insomnia or other sleeping disorders?
□ No at all
□ Mild or temporary sleeping disorders
□ Moderate sleeping disorders
□ Severe sleeping disorders

What kind of sleep-related problems? _____

If you have suffered from insomnia or sleeping disorders, how have they been treated?
□ Not treated □ As needed: _____ □ Regular: _____ □ _____

HEALTH HABITS

Weight: _____ Height:_____

It is important to get enough vitamins and minerals. Is your diet balanced? (Issues relating to diet and nutrition can be documented here)

_____

Are you able to exercise (outdoors) regularly? (Issues relating to exercise can be documented here)

_____

Alcohol may change the effects of some drugs. Do you use alcohol?
□ No □ Yes

If yes, how often:
□ once a month or less □ 2-4 times a month □ 2-3 times a week □ more than 4 times a week

How many doses of alcohol do you use at once (one dose corresponds to one bottle of beer or cider, 12 cl of wine, 8 cl strong wine, 4 cl of spirits (40%)
□ 1-2 □ 3-4 □ 5-6 □ 7-9 □ more than 10 doses

Smoking may adversely affect treatment of some conditions or change drug effects. Do you smoke?
□ No □ Yes, for ____ years □ Quit____ years ago

If yes, how many cigarettes per day?
□ less than 10 □ 11-20 □ 21-30 □ more than 30 cigarettes

*If you have any other concerns or questions regarding your drug treatment, please feel free to ask. Up-coming issues can be documented here:

_____

_____

_____

Reporting: _____ □ Written report for the patient
Decision on the timetable of follow-up: _____

[a] Formulation of questions modified from the UKU side effect rating scale (Lingjaerde et al. 1987) or its version for patient self-administration; UKU-SERS-Pat (Lindström et al. 2001)

Appendix 3. CMR Referral and Patient Data Collection Form

REFERRAL AND PATIENT DATA COLLECTION FORM

Name	Identity number
Physician	Date of data collection
GROUNDS FOR REFERRAL	

HEALTH STATE AND MEDICATIONS

Complete as appropriate, medication chart/patient records may be attached

DISEASE STATE/ DIAGNOSES (e.g., diabetes)	**MEDICATIONS, OTHER TREATMENT** (e.g., diet/metformin)	**STRENGTH, DOSING** (e.g., 500 mg x 2 before meal)	**THERAPEUTIC GOAL**	**OTHER INFORMATION**

LABORATORY TEST RESULTS (e.g., blood pressure, serum electrolytes etc., if relevant)

TEST	**DATE**	**RESULT**	**THERAPEUTIC GOAL**

OTHER NOTIFICATIONS (e.g., allergies, swallowing difficulties):

_____

_____

_____

_____

Appendix 4. CMR Case Report

COMPREHENSIVE MEDICATION REVIEW

Name	Identity number
Address	Physician
Assignment / grounds for the review	

SHORT SUMMARY OF PATIENT CLINICAL DATA

Diagnoses:

Medication list (or drug chart as an attachment)

- Regular:
- As needed:

Relevant laboratory test results and therapeutic goals

Test	Result	Goal	Note
Blood pressure		General goal <140/85 mmHg	Diabetics and other high-risk patients <130/80 mmHg
BG (feasting) BG (after meal)		4-6 < 8	
Hb1Ac		< 6-7	If no hypoglyceamias
Hb		>120 ♀ >130 ♂	
Chol LDL HDL Trigly		<5 <3 >1 <2	great risk (e.g., diabetes) <4.5 great risk <2,5 (if arterial events <1.8)
Krea GFR		♀: 50-90 ♂: 60-100 > 90 ml/min (mild 60-89, modest 30-59, severe 15-29)	GRF= ♀: (140 – age) x weight / 0,95 x P-krea (µmol/l). ♂: (140 – age) x weight / 0,8 x P-krea (µmol/l).
Other			

SUMMARY OF NURSE'S / CARETAKER'S COMMENTS

SUMMARY OF PATIENT INTERVIEW ___.___**.201**__ *(Drug use, DRPs, adherence, adverse drug reactions, pain, living habits etc.)*

Symptom	**Severity**			**Frequency**	**Current treatment**
	mild	remarkable	severe		
Dryness of mouth					
Constipation					
Urinary disturbances					
Pain					
Insomnia/sleep disorders					
Dizziness					
Falls					
Confusion					
Other:					

Adherence:

□ Date of follow-up: _____.201_ □ A written report for the patient

Appendix 4. Continued.

FINDINGS

Reimbursements and economical issues *(Special reimbursements, generic substitution...)*

Duplication / interactions

Product	Interaction class (A-D, 1-4)	Clinical significance
/		
/		
/		

Anticholinergic drugs:
Serotonergic drugs:
Sedative drugs:

Inappropriate drugs / doses / treatment duration *(= in regard to conditions / age / care guidelines, potential adverse effects, as needed drug in regular use, needed drug not in use/prescribed…)*

Treatment of patient's most significant conditions *(e.g., compliance with care guidelines, meeting of therapeutic goals, appropriateness of drug choices and dosage…)*

MOST IMPORTANT FINDINGS AND RECOMMENDATIONS

Recommendation	Justification / grounds	Physician's comments __.__.201_

_____ __ / __ 201_ _____
reviewer

CHANGES AGREED ON DRUG REGIMEN *(drugs added, stopped, doses changed)*

IMPLEMENTATION OF ACTIONS *(who, how, when)*

DURATION OF CMR
Groundwork ____, interview ____, review ____, case conference ____ = Total _____

SUMMARY OF FOLLOW-UP INTERVIEW ___.___.201__

DRUG COSTS (for 3 months supply)

Before CMR _____, after changes _____, after follow-up _____

Appendix 5. CMR Review Chart

REVIEW CHART **Patient: _____**

Drug: brand name, strength	Active ingredient	Dose	Drug chart/ dosing M D A E N	Purpose of use / clinical condition (date started)	Note!	CYP (substr./ inhib./ induct.)	Other interaction	Lab tests required	Sed.	AC +/-	SS +/-	RR ↑/↓	HR ↑/↓	BG ↑/↓	K+ ↑/↓	QT +/-	Other (ADRs, Na+ …)	Other information

Abbreviations:
Sed. = sedative properties
BG = effect on blood glucose
RR = effect on blood pressure
HR = effect on heart rate
SS = serotonergic effects
QT = effect on QT-time
AC = anticholinergic effect
K+ = effect on serum potassium
Other = e.g., relating to the cause for referral (e.g., dizziness, falls, nausea)

Appendix 6. EQ-5D Finnish version (Descriptive system and the Visual Analoque Scale)

Olkaa hyvä ja merkitkää rastilla (x), yksi rasti kunkin alla olevan ryhmän kohdalle, mikä väitteistä kuvaa parhaiten terveydentilaanne tänään:

Liikkuminen

- Minulla ei ole vaikeuksia kävelemisessä ❑
- Minulla on jonkin verran vaikeuksia kävelemisessä ❑
- Olen vuoteenomana ❑

Itsestään huolehtiminen

- Minulla ei ole vaikeuksia huolehtia itsestäni ❑
- Minulla on jonkin verran vaikeuksia peseytyä tai pukeutua itse ❑
- En kykene peseytymään tai pukeutumaan itse ❑

Tavanomaiset toiminnot *(esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot)*

- Minulla ei ole vaikeuksia suorittaa tavanomaisia toimintojani ❑
- Minulla on jonkin verran vaikeuksia suorittaa tavanomaisia toimintojani ❑
- En kykene suorittamaan tavanomaisia toimintojani ❑

Kivut/vaivat

- Minulla ei ole kipuja tai vaivoja ❑
- Minulla on kohtalaisia kipuja tai vaivoja ❑
- Minulla on ankaria kipuja tai vaivoja ❑

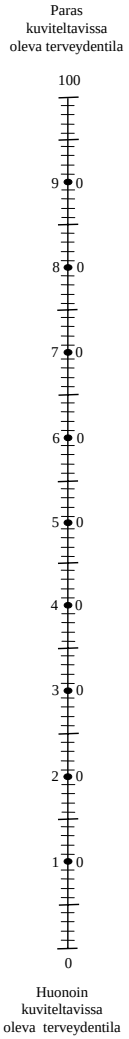
Ahdistuneisuus/Masennus

- En ole ahdistunut tai masentunut ❑
- Olen melko ahdistunut tai masentunut ❑
- Olen erittäin ahdistunut tai masentunut ❑

Auttaaksemme ihmisiä sanomaan, kuinka hyvä tai huono jokin terveydentila on, olemme piirtäneet lämpömittaria muistuttavan asteikon. Parasta terveydentilaa, jonka voitte kuvitella, merkitään siinä 100:lla ja huonointa 0:lla.

Haluaisimme Teidän osoittavan tällä asteikolla, miten hyvä tai huono Teidän terveytenne on mielestänne tänään. Olkaa hyvä ja tehkää tämä vetämällä alla olevasta laatikosta viiva siihen kohtaan asteikolle, joka osoittaa, miten hyvä tai huono terveydentilaanne on tänään.

Terveydentilani tänään



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