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Development and Validation of a Drug-Related Problem Risk Assessment Tool for Use by Practical Nurses Working with Community-Dwelling Aged

Maarit Dimitrow

ACADEMIC DISSERTATION

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Non scholae sed vitae discimus

Abstract

The demand for long-term home health care services for the aged (≥65 years) is growing. Aged people needing home care (HC) are increasingly older, have many chronic diseases and use multiple medicines, and thus, are at a high risk for drug-related problems (DRPs). Practical nurses (PNs) are those who most often visit the aged using HC services and consequently, are in a key position to monitor the expected positive outcomes and risks of pharmacotherapy of their clients.

The aim of this study was to develop and validate an easy-to-use DRP Risk Assessment Tool (DRP-RAT) for PNs caring for home-dwelling aged ≥65 years focusing on identifying and solving the highest priority DRP risks. The specific aims were: 1) to systematically review articles that describe criteria for assessing inappropriate prescribing in the aged ≥65 years; 2) to describe the development process and content validation of the DRP-RAT; 3) to evaluate the feasibility of the final DRP-RAT among PNs in HC; and 4) to assess the reliability of risk assessments conducted by PNs by using DRP-RAT and to identify the clinically most significant DRPs needing action.

This study applied both quantitative and qualitative methods. Original English language articles were systematically searched on MEDLINE and PubMed, with a time restriction of 1.1.1990–17.6.2010, focusing on the development methods and contents of the criteria for potentially inappropriate prescribing for the aged (Study I, year 2010). Two systematic literature reviews (Study I, an unpublished one) and the expertise of the research group were used as a basis for the development of the DRP-RAT. The content of the draft tool was validated by a three-round Delphi survey with a panel of 18 experts in geriatric care and pharmacotherapy (Study II, year 2010). Data for the feasibility study were collected during the training of PNs, working in HC, in the use of the DRP-RAT (Study III, year 2011). For Study III, an analysis was made of the PN-conducted (n=25) DRP risk assessments of their self-selected clients by DRP-RAT (n=85) and the same clients' copied medication lists (n=68), face-to-face discussions and responses to open questions of the returned feedback forms (n=23). In 2013, an experienced geriatrician reviewed HC clients' (n=45) medications by using three different reviewing methods on each patient (Study IV, year 2013). The methods based on: 1) DRP-RAT (n=45) completed by the PNs (n=26) and copied medication lists; 2) health centre's medical records ("gold standard"); and 3) Methods 1 and 2 together. Results of the reviews and contents of the geriatrician's open comments regarding the PNs' risk assessments were analyzed. DRPs in the study population identified and reported by the geriatrician were studied from the geriatrician's DRP classifications (n=45) and by a retrospective review of the geriatrician's case reports (n=45).

Most of the criteria were explicit (10 out of 14), consensus validated, based totally or partly on Beers criteria, and focused on pharmacological appropriateness of prescribing. The majority represented a quantification of misprescribing, e.g., potentially inappropriate medications, most common harmful drug-drug and drug-disease interactions and related potential geriatric-specific adverse effects. The final DRP-RAT consisted of 18 items that

assess risks for DRPs in home-dwelling clients. It is divided into four sections: 1) Basic Client Data, 2) Potential Risks for DRPs in Medication Use, 3) Characteristics of the Client's Care and Adherence and, 4) Recommendations for Actions to Resolve DRPs. PNs spent on average 20±8 minutes reviewing one client's medication using the DRP-RAT and reliably identified 88% of the risk medicines used by their clients listed in the tool. Of the respondents (n=23) of the feedback forms, 43% reported it was easy or quite easy to answer the questions of the DRP-RAT. Generic names of medicines, time constraints, home-care workers' and/or clients' lack of interest to clients' pharmacotherapy and short client contacts were the most common barriers to using the tool. The DRP-RAT completed by the PNs was capable of providing reliable and timely patient information to support physician's clinical decision making. Compared to the "gold standard" (Method 2), Method 1 resulted in a false negative rating in 7% (95 % CI 1.4–18.3) of the cases (3/45). The geriatrician identified an average of 3.1 potential DRPs per patient.

This study indicates that the DRP-RAT, developed and validated in this study, could make it possible to more effectively involve PNs, working in HC, in medication risk management among the home-dwelling aged, and that medication risk management should be focused on the highest priority risks. Unlike existing nurse-administered risk assessment tools focusing mainly on issues relating to adherence and medication management, the DRP-RAT focuses on the highest priority risks related to the pharmacological effects of the medications but also on factors related to the medication use process. Integrating training to use the DRP-RAT into PN curricula is important. Actions to facilitate the implementation of the DRP-RAT in the Finnish health care system are needed. Future studies are needed to evaluate the effects of PNs' risk assessments using the DRP-RAT on clinical, humanistic and economic outcomes.

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II Dimitrow M, Mykkänen S, Leikola S, Kivelä S-L, Lyles A, Airaksinen M. Content validation of a tool for assessing risks for drug-related problems to be used by practical nurses caring for home-dwelling clients aged ≥65 years: A Delphi survey. Eur J Clin Pharmacol 2014;70:991–1002.

III Dimitrow M, Leikola S, Kivelä S-L, Passi S, Lukkari P, Airaksinen M. Feasibility of a practical nurse administered risk assessment tool for drug-related problems in home care. Scand J Public Health 2015;43:761–769.

IV Dimitrow M, Puustinen J, Viikari P, Uutela E, Vahlberg T, Airaksinen M, Kivelä S-L. Can practical nurses identify aged home care patients at risk of drug-related problems – geriatrician's appraisal of their risk assessments (submitted)

The publications are referred to in the text by their roman numerals. Reprinted with the permission of the copyright holders.

Definitions of the key concepts

Adverse drug event (ADE)
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 medicine, and any harm secondary to a medication error, both errors of omission or commission (Council of Europe 2006a).

Adverse drug reaction (ADR)
A response to a medical product which is noxious and unintended, and occurs at doses normally used in man (Council of Europe 2006a).

Adverse event (AE)
An unintended injury caused by medical management rather than by a disease process (Council of Europe 2006a).

Culture of safety
An integrated pattern of individual and organizational behavior, based upon shared beliefs and values, that continuously seeks to minimize patient harm which may result from the processes of care delivery (Council of Europe 2006a).

Deprescribing
Tapering, reducing or stopping a medication (Farrell et al. 2015).

Drug-Related Problem (DRP)
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 widely used definition for DRP is "An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (PCNE 2010). Often used as a synonym of the term "drug-therapy problem" 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). In this thesis, DRPs are discussed (if not otherwise mentioned) on the basis of the definition of the PCNE 2010 (PCNE 2010).

Cause (process) of a drug-related problem
The process leading to a drug-related problem can be understood as a failure associated with the process of medicine use (Basger et al. 2014). It can also be defined as an action (or lack of action) that leads to the occurrence of a potential or real problem (PCNE 2010). There may be more than one causes for each problem. Medication errors may be named as causes of DRPs (PCNE 2010), or medication errors can be causes of risks to DRPs (Council of Europe 2006a).

Geriatric pharmacotherapy
Tailored pharmacotherapy for the aged taking into account aged-related body changes that affect how medicines are handled. Most often used age-limits are: ≥65 years or ≥75 years (AGS 2015, Finnish Medicines Agency 2015a).

Home care
In Finland a Health Centre is a primary care unit and part of the public health care system, which is the dominating health care system covering the entire population through public social insurance (Teperi et al. 2009). Health centres offer a wide variety of services, including home care. Municipal home care services encompass social and health services including home help and home nursing. Home care services for the aged are nearly always provided as long-term services. In this thesis, when discussing home care it is preferred to term home nursing.

Inappropriate prescribing
A situation in which the pharmacotherapy does not meet accepted medical standards (Hanlon et al. 2001).

Medication adherence
The extent to which a person's behaviour in taking medicines corresponds with the agreed recommendations from a health care provider (WHO 2003).

Medication error
Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is under the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use (NCC MERP 2016).

Medication review
A structured evaluation of patient's medicines with the aim of optimizing medicine use and improving health outcomes. This entails detecting drug-related problems and recommending interventions (PCNE 2016a). Medication review procedures may differ in comprehensiveness and in the levels of multiprofessional collaboration (Clyne et al. 2008, Leikola 2012).

Medication safety
Medication safety refers to quality and safety of pharmacotherapy. Medication safety comprises both adverse drug reactions (product safety) and medication errors (safety of health-care services) (STAKES and ROHTO 2006). Defined also as 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 2006a).

Medication use system
A combination of interdependent processes that share the common goal of safe, effective, appropriate, and efficient provision of medicine therapy to patients. Major processes in the medication use system are: selecting and procuring; storage; prescribing; transcribing and verifying/reviewing; preparing and dispensing; administering and monitoring (Council of Europe 2006a).

Patient safety
Patient safety is the prevention of errors and adverse effects to patients associated with health care (WHO 2016). Also defined as the identification, analysis and management of patient-related risks and incidents, in order to make patient care safer and minimize harm to patients (Council of Europe 2006a).

Potentially inappropriate medication (PIM)
In this thesis, the term potentially inappropriate medication refers to medication that is considered to be inappropriate for individuals aged 65 years and older. It is considered as inappropriate because of questionable efficacy, unfavorable benefit-risk or because safer alternatives exist (Beers et al. 1991, Fick et al. 2003, AGS 2015).

Practical nurse
Health care professional having three years vocational education that concentrates mainly on supporting and technical nursing (Finnish National Board of Education 2010).

Risk assessment
The process that helps organizations understand the range or risks that they face both internally and externally, the level of ability to control those risks, the likelihood of occurrence and their potential impacts. It involves a mixture of quantifying risks and using judgement, assessing and balancing risks and benefits and weighing them for example against cost (Council of Europe 2006a).

Risk management
Clinical and administrative activities undertaken to identify, evaluate, and reduce the risk of injury to patients, staff, and visitors and the risk of loss to the organization itself (Council of Europe 2006a).

System
A set of interdependent elements interacting to achieve a common aim. These elements may be both human and non-human (equipment, technologies) (Council of Europe 2006a).

Systems approach
A system-based approach presupposes the systematic design of safe structures, procedures and processes, together with corrective reactions in response to safety incidents. It is

accepted that errors are a consequence of normal human fallibility and/or deficiencies of the system; these could be prevented by improving the conditions in which humans work. The aim is a system designed with built-in defences (Council of Europe 2006b).

Abbreviations

AACP	Australian Association of Consultant Pharmacy
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ADD	Automated Dose Dispensing
AFP	Association of Finnish Pharmacies
AGS	American Geriatric Society
AOU	Assessment of Underutilization of Medication
APhA	American Pharmacists Association
CGA	Comprehensive Geriatric Assessment
ChEI	Cholinesterase Inhibitor
CMR	Comprehensive Medication Review
CNS	Central Nervous System
DAP	Drug with Anticholinergic Properties
DDI	Drug-Drug Interaction
DN	District Nurse
DMMR	Domiciliary Medication Management Review (Australia)
DRP	Drug-Related Problem
DRP-RAT	Drug-Related Problem Risk Assessment Tool
DTP	Drug Therapy Problem
DUR	Drug Utilization Review (USA)
GheOP^{3}S Tool	Ghent Older People's Prescriptions community Pharmacy Screening Tool
GI	Gastrointestinal
GP	General Practitioner
HMR	Home Medicines Review (Australia)
IPET	Improving Prescribing in the Elderly Tool
MAI	Medication Appropriateness Index
MR	Medication Reconciliation
MRAQ	Medication Risk Assessment Questionnaire
MRP	Medication-Related Problem
MTR	Medication Therapy Review (in MTM)
MTM	Medication Therapy Management (US)
MUR	Medication Use Review (England, Wales)
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention (US)
NORGEP	Norwegian General Practice
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-The-Counter
PCNE	Pharmaceutical Care Network Europe
PIM	Potentially Inappropriate Medication
PN	Practical Nurse
PPI	Proton Pump Inhibitor

PREVENT	**P**hysical impairment, **R**isk from specific med/medicines related admission, adh**E**rence issues, cogniti**V**e impairment, n**E**w diagnosis/exacerbation of disease, compli**N**ce, socie**T**al/social – Risk Indicator for Medicines-related Problems
RCT	Randomized Controlled Trial
RMMR	Residential Medication Management Review (Australia)
ROHTO	National Centre for Pharmacotherapy Development
SFINX	**S**wedish, **F**innish, **IN**teraction **X**-referencing
SII	Social Insurance Institution of Finland
SMA Tool	Swedish Safe Medication Assessment Tool
SSRI	Selective Serotonin Reuptake Inhibitor
STAKES	National Research and Development Centre for Welfare and Health
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions
TIPPA	Tarkoituksenmukainen Informaatio Potilaan Parhaaksi Apteekista: Customized Information for the Benefit of the Patient from the Community Pharmacy
WHO	World Health Organization

1 Introduction

Medication risk management has become an increasingly more important area of research during the last decades. This is because medication use has become more common, leading to complex medications particularly among the aged. According to the Act on Supporting the Functional Capacity of the Older Population and on Social and Health Care Services for Older Persons (980/2012) an "older person" is "a person whose physical, cognitive, mental or social functional capacity is impaired due to illnesses or injuries that have begun, increased or worsened with high age or due to degeneration related to high age". From the pharmacological approach aged people can be considered as "a special population" differing from younger adults in terms of comorbidity, polypharmacy, pharmacokinetics and pharmacodynamics. Due to age-related body changes and other factors related to aging (e.g., memory problems, impaired hearing and/or vision, impaired cognition) older people as medicine users are vulnerable to a wide range of drug-related problems which makes prescribing for the aged challenging.

Drug-related problem (DRP) can be defined as *"an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"* (PCNE 2010). Terms drug-therapy problem (DTP) (Cipolle et al. 2004) and medication-related problem (MRP) (APhA and NACDS Foundation 2008) are often used as synonyms to DRP. Of the single type of DRPs adverse-drug reactions (ADRs) are among the most common to result in severe harm (Pirmohamed et al. 2004, Patel et al. 2007, van der Hooft et al. 2008, Pedrós et al. 2016). A recent systematic review showed that in primary care, patient safety incidents resulting in severe harm were most often related to diagnosis and prescribing, and typically occurred among the aged or those taking multiple medications (Panesar et al. 2015).

It is estimated that over a half of the harmful medication incidents could be prevented with more active and systematic risk management during the entire medication use process (Panesar et al. 2015). This has resulted in a need to develop and implement methods for identifying and solving, but also preventing, DRPs. As the medication safety risks are found to cumulate with older medicine users (Panesar et al. 2015) a growing number of risk management methods are specifically designed for the aged.

The focus of this doctoral thesis is the development and validation of a Drug-Related Problem Risk Assessment Tool (DRP-RAT) for use by practical nurses (PNs) taking care of home-dwelling clients ≥65 years, with the aim of involving PNs working with aged home care clients in medication risk management. The literature review of this thesis (Chapters 2–3) aims to provide a conceptual and theoretical background for the empirical research. International and national strategies and tools to prevent and resolve DRPs in geriatric pharmacotherapy are introduced in Chapters 4 and 5. Chapter 6 represents an overview of Finnish studies which aim to identify and resolve problems related to medicine use of the aged.

2 Drug-related problems

The concept "inappropriate use of medicines" comprises several different improper ways to use medicines, which potentially lead to DRPs (Figure 1).

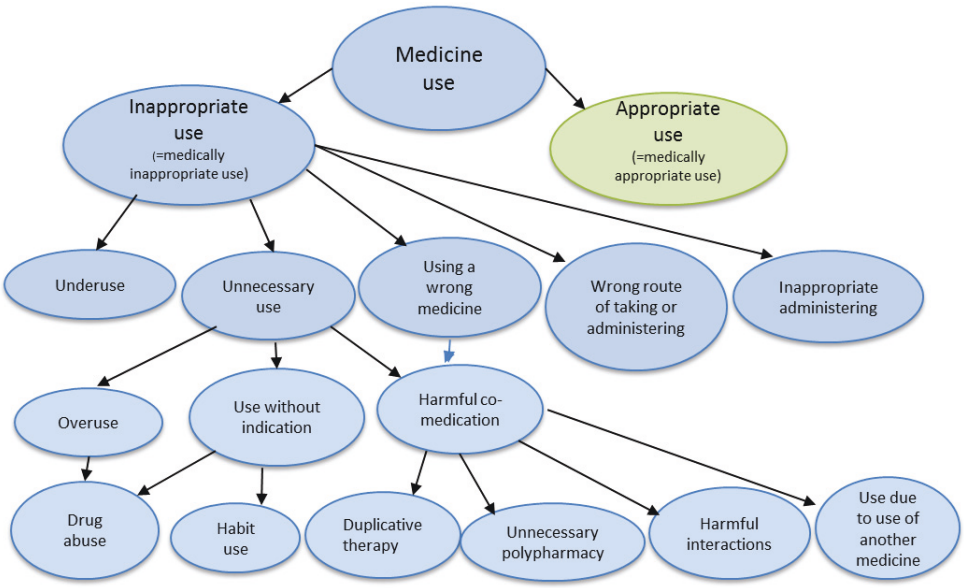

Figure 1 *Drug-related problems can occur for many reasons during the medication use process (STAKES and ROHTO 2006)*

Through time, researchers have tried to understand factors leading to inappropriate use of medicines, potential problems resulting from inappropriate medicine use and their prevention. This has resulted in the development of standardized DRP classification systems, the first of which was the Strand classification developed in the US by Strand and colleagues (Figure 2, Table 1) (Strand et al. 1990, Basger et al. 2014). The Strand classification was an essential part of the philosophy of pharmaceutical care launched by Charles Hepler and Linda Strand from the University of Florida in 1990 (Hepler and Strand 1990). The core element of the philosophy and practice of pharmaceutical care is to identify, solve and prevent DRPs in cooperation with a patient and other health care professionals. According to this philosophy, in addition to dispensing medicines, pharmacists are also responsible for monitoring medicine treatments and evaluating their outcomes. The philosophy extends quality assurance principles and systems thinking to clinical pharmacotherapy in patient care and emphasizes the integration of drug therapy with other elements of care.

The aim of this Chapter is to describe milestones in the development of DRP classification systems since 1990 when the first classification system was launched (Strand et al. 1990, Figure 2).

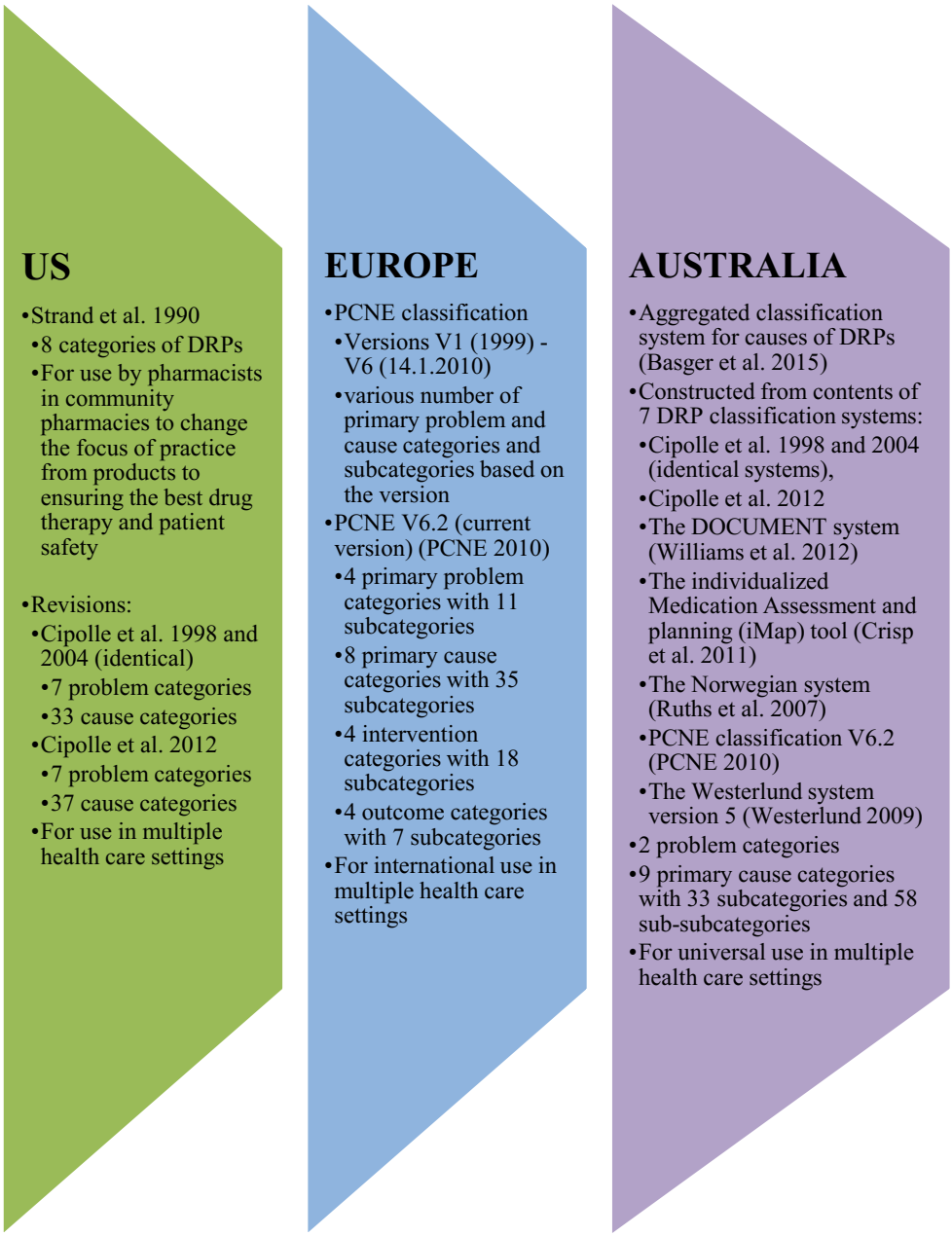

Figure 2 *Milestones in development of DRP classification systems since 1990 when the first classification system was launched by Hepler and Strand (Hepler and Strand 1990)*

2.1 Drug-related problem (DRP) classification systems

Since the launch of the Strand's DRP classification in 1990 (Strand et al. 1990, Hepler and Strand 1990), researchers in different countries have developed several classification systems for DRPs and their causes (Basger et al. 2014, Figure 2). These systems differ e.g., in definitions of DRPs; a recent systematic literature review by Basger and colleagues (2014) identified altogether twelve definitions of DRPs, the majority mixing both process of drug use (or cause) and outcome (or problem). This has resulted in differences in the number and contents of problem and cause categories. For example, the problem identified in the PCNE Classification V6.2 "The patient suffers from an ADR at normal dose or from a toxic reaction" is the same as the sub-cause "An adverse drug reaction occurred" in Basger's classification of causes of DRPs (PCNE 2010, Basger et al. 2015).

Over time, the classifications have moved towards integrating causes of DRPs as an essential part of the classification system (Figure 2), indicating the importance of understanding causes for building up safer medication use processes and preventing DRPs to occur. This is in line with the current systems thinking in patient safety in which deficiencies in medication safety have been prioritized as the most important single factor jeopardizing patient safety (Council of Europe 2006a). The classifications can be used in clinical practice to document the nature, prevalence, and incidence of DRPs, but also as process indicators in medication safety research.

2.1.1 The Strand classification

The Strand classification was originally developed to enhance pharmacist's involvement in ensuring the optimum drug therapy and patient safety (Figure 2, Table 1) (Strand et al. 1990). The classification served as an aid in the development of standards of practice for pharmacists. Strand and colleagues defined DRP as "an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome". Eight categories of DRPs were identified (Strand et al. 1990, Table 1). Problems and causes were not separated in this classification. Later, the classification was revised by renaming DRPs as DTPs (Drug-Therapy Problems), also drug interactions were removed from problem category to cause category as they were considered as causes for DTPs (Cipolle et al. 1998, Cipolle et al. 2004). Thus, the revised classification included 7 problem categories and 33 cause categories (Figure 2). The latest revision of the classification includes 7 problem categories and 37 cause categories (Cipolle et al. 2012).

Table 1. *Categories of Drug-related Problems (DRPs) in the original classification system by Strand et al. (1990)*

DRP category and definition
1. ***Untreated indication***   The patient has a medical condition for that requires drug therapy (a drug indication) but the patient is not receiving a drug for that indication
2. ***Improper drug selection***   The patient has a medical condition for which the wrong drug is being taken
3. ***Subtherapeutic dosage***   The patient has a medical condition for which too little of the correct drug is being taken
4. Overdosage   The patient has a medical condition for which too much of the correct drug is being taken
5. Adverse drug reaction   The patient has a medical condition resulting from an adverse drug reaction
6. ***Drug-interactions***   The patient has a medical condition resulting from a drug-drug, drug-food, drug-laboratory interaction
7. Failure to receive drugs   The patient has a medical condition that is the result of not receiving the prescribed drug
8. 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

2.1.2 Pharmaceutical Care Network Europe (PCNE) classification system

Another landmark in the DRP classification systems is the European PCNE classification (PCNE 2010, Figure 2, Table 2). Pharmaceutical Care Network Europe (PCNE) started under WHO EuroPharm Forum and was established in 1994 by European pharmaceutical care researches (PCNE 1999). PCNE became an independent official association (under Dutch law) in 2004.

Knowing the variability between previous DRP classification systems the development of the PCNE classification aimed at a comprehensive standardized system that could be used in international studies to ensure comparable results (van Mil et al. 2004a, Figure 2). The first PCNE classification system for DRPs was constructed in 1999 during the working conference of PCNE (PCNE 1999). Later, the DRP system has been validated and updated regularly, the latest version (V6.2) being updated in 2010 with the following DRP definition: ***"A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"*** (PCNE 2010). Currently, this hierarchical classification lists 4 primary DRP categories: 1) (potential) problems with

the (lack of) effect of the pharmacotherapy; 2) patient suffers, or will possibly suffer, from an adverse drug event; 3) the drug treatment is more expensive than necessary; or 4) others, with altogether 11 subcategories. The classification system also includes 8 primary and 35 subcategories for causes of DRPs, and 5 primary and 18 subcategories for interventions that the problems can lead to in order to correct the cause(s). Furthermore, the system has an outcome section to indicate if the problem has been solved. The 5th working symposium of PCNE was held in February 2016. Among other matters, the workshop started working on version 7.0 of the classification (PCNE 2016b).

In addition to research purposes DRP classifications are applicable to clinical practice. E.g., in Finland, a modified version of the PCNE classification 5.01 and later a slightly modified version V6.2 have been used as part of the collaborative comprehensive medication review (CMR) procedure which has been in use since 2005 (Leikola et al. 2009, Leikola et al. 2012a, Leikola et al. 2012b, Leikola 2012). So far, about 200 pharmacists have been accredited to conduct CMRs in Finland (Leikola et al. 2016).

2.1.3 Recent developments: An aggregated system for classifying causes of drug-related problems

A recent systematic literature review identified 20 different types of DRP classification systems and their modifications developed during the last 25 years (Basger et al. 2014 and 2015). Wide variability between the systems found results in the lack of a comprehensive and universally acceptable classification system making study comparisons difficult. Noticing this lack Basger and colleagues performed a category-by-category comparison of the content of seven selected DRP classification systems (Cipolle et al. 2004, Westerlund 2009, PCNE 2010, Grisp et al. 2011, Ruths et al. 2011, Williams et al. 2011, Cipolle et al. 2012) in modified or unmodified form in order to construct an aggregated cause-of-DRP classification system containing the content of all systems (Basger et al. 2015, Figure 2). The PCNE Classification V6.2 was used as a template for the analysis (Basger et al. 2015). Those seven systems were identified after the previous literature review (Basger et al. 2014) and were selected based on their use in various health care settings, developing country, frequency of use, and development methods (Basger et al. 2014 and 2015). The resulting hierarchical system has two categories for actual or potential DRPs: 1) drug treatment goals are not reached (i.e., the drug does not work) and 2) drug treatment causes an undesirable effect or effects (i.e., the drug causes harm). It encompasses 9 cause-of-DRP categories with 33 subcategories, and 58 sub-subcategories (Table 2). This new categorization may provide the most comprehensive description of causes of DRPs to date.

Recent classifications have a broad approach to DRPs as they comprehensively identify different factors that (potentially) cause negative outcomes related to the whole medicine use system. The more detailed the cause categories are the more easy it is to understand that the causes potentially leading to DRPs may occur at every step of the medicine use process

and may be related to each individual dealing with the patient's pharmacotherapy as well as to medicine.

Table 2 gathers causes of DRPs listed in the PCNE classification V6.2 (PCNE 2010) and in Basger's aggregated classification system (Basger et al. 2015). They are (re)grouped according to factors (patient, carer, nurse, physician, medicine and pharmacist) that they may be related to. It is notable that one cause can be related to several factors. According to the current understanding and classifications (Basger et al. 2015), the cause of DRP can be in prescribing (e.g., selection of the drug, drug form or dosing), in the way in which the patient selects or uses the drug or in the way in which it has been administered, in supply (e.g., dispensing, drug not available, transferring error), in monitoring (e.g., too frequent or too infrequent monitoring, inappropriate test ordered), or an ADR has occurred or there may be no obvious reason for treatment failure.

Table 2. *Causes leading to drug-related problems (DRPs) from PCNE Classification V6.2 (2010) and Basger's aggregated classification system (Basger et al. 2015) (re)grouped according to factors they may be related to. Both classifications have systems approach to causes of DRPs.*

HEALTH CARE STAFF RELATED FACTORS		
Prescriber-related factors		
Causes of DRPs according to The PCNE Classification V6.2 (2010)	**Causes of DRPs according to the Aggregated System Category by Basger et al. (2015)**	
C1 Drug selection	**1. Drug selection**	
C1.1 Inappropriate drug (incl. contra-indicated)	1.1 Inappropriate drug due to contraindication, ineffectiveness, regimen (regular rather than "when required") or safer alternative available	1.1.1. Precaution with the use of this drug 1.1.2. Drug (absolutely) contraindicated 1.1.3. An unnecessary drug is taken because of the use of another drug 1.1.4. Drug is not the most safe/effective treatment for the patient's medical condition according to guidelines 1.1.5. Drug is not effective for the indication being treated 1.1.6. Medical condition is refractory to drug
C1.2 No indication for drug	1.2 No indication for drug	1.2.1. No (documented) indication apparent 1.2.2. No indication due to duplication 1.2.3. Indication does not warrant drug treatment
C1.3 Inappropriate combination of drugs, or drugs and food	1.3 Inappropriate combination of drugs, or drugs and food, or drugs and alcohol	1.3.1. A drug interaction may cause/causes an undesirable reaction by increasing the therapeutic effect of one or both drugs 1.3.2. A drug interaction may cause/causes an undesirable reaction by decreasing the therapeutic effect of one or both drugs 1.3.3. A drug interaction may cause/causes a hypersensitivity reaction
C1.4 Inappropriate duplication of therapeutic group or active ingredient		
C1.5 Indication for drug-treatment not noticed	1.4 Indication not treated/missing therapy	
C1.6 Too many drugs prescribed for indication		
C1.7 More cost-effective drug available	1.5 More cost-effective drug available	
C1.8 Synergistic/preventive drug required and not given	1.6 Synergistic/preventive drug required and not given	1.6.1. Preventive drug therapy is required to reduce the risk of developing a new condition 1.6.2. A medical condition requires additional pharmacotherapy to attain synergistic or additive effects
C1.9 New indication for drug treatment presented		

C2 Drug form	**2. Drug form**	
C2.1 Inappropriate drug form	2.1 Inappropriate or suboptimal drug form	
C3 Dose selection	**3. Dose selection**	
C3.1 Drug dose too low	3.1 Drug dose too low	
C3.2 Drug dose too high	3.2 Drug dose too high	
C3.3 Dosage regimen not frequent enough	3.3 Dosage regimen not frequent enough	
C3.4 Dosage regimen too frequent	3.4 Dosage regimen too frequent	
C3.5 No therapeutic drug monitoring		
C3.6 Pharmacokinetic problem requiring dose adjustment		
C3.7 Deterioration/improvement of disease state requiring dose adjustment	3.5 Deterioration/improvement of disease state requiring dosage adjustment	3.5.1. Deterioration of disease state requiring dosage adjustment 3.5.2. Improvement of disease state requiring dosage adjustment
	3.6 Dosage instructions unclear, incomplete, or not understood by patient/carer	
C4 Treatment duration	**4. Treatment duration**	
C4.1 Duration of treatment too short	4.1 Duration of treatment too short	
C4.2 Duration of treatment too long	4.2 Duration of treatment too long	
	5. Drug use process	
	5.2 Drug underused/underadministered	5.2.8. The drug was underadministered by the health care professional (doctor)
	5.3 Drug overused/overadministered	5.3.4. The drug was overadministered by carer or health care professional (doctor)
	6. Logistics	
	6.1 Prescribed drug not available	6.1.3. A drug order does not meet legislative requirements
	6.2 Drug order incorrect, incomplete, poorly legible/illegible or discrepant (also known as transferring errors)	6.2.1. A drug order is incorrect or incomplete 6.2.2. Drug order/transition of care discrepancy 6.2.3. The way in which information/directions were written caused the patient/carer to misuse the drug
	6.3 Error in drug selection	6.3.1. Doctor chooses the wrong drug
	7. Monitoring	
	7.1 Monitoring too frequent	7.1.1. Monitoring of disease state too frequent 7.1.2. Therapeutic drug monitoring too frequent 7.1.3. Monitoring for the effect/adverse effect of drug too frequent
	7.2 No or too infrequent monitoring	7.2.1. Monitoring of disease state absent or too infrequent 7.2.2. Therapeutic drug monitoring absent or too infrequent

		7.2.3. Monitoring for the effect/adverse effect of drug absent or too infrequent 7.2.4. Monitoring may have occurred but is unavailable or not documented
	7.3 Inappropriate test ordered	
Nurse-related factors		
Causes of DRPs according to The PCNE Classification V 6.2 (2010)	**Causes of DRPs according to the Aggregated System Category by Basger et al. (2015)**	
	5. Drug use process	
	5.1 Inappropriate timing of administration and/or dosing intervals by nurse	
	5.2 Drug underused/underadministered	5.2.8. The drug was underadministered by the health care professional (nurse)
	5.3 Drug overused/overadministered	5.3.4. The drug was overadministered by carer or health care professional (nurse)
	5.7 Nurse unable to use/does not use drug/form as directed	
	5.8 Adequate information not provided or not understood or misunderstood or not followed	5.8.1. Adequate information about drug not provided 5.8.2. Incorrect information about drug provided 5.8.3. Adequate information about disease state management not provided or not understood or not followed 5.8.4. Incorrect information provided about disease state
	6. Logistics	
	6.3 Error in drug selection	6.3.3. Nurse administers drug from the wrong patient's drug chart
	7. Monitoring	
	7.1 Monitoring too frequent	7.1.1. Monitoring of disease state too frequent 7.1.2. Therapeutic drug monitoring too frequent 7.1.3. Monitoring for the effect/adverse effect of drug too frequent
	7.2 No or too infrequent monitoring	7.2.1. Monitoring of disease state absent or too infrequent 7.2.2. Therapeutic drug monitoring absent or too infrequent 7.2.3. Monitoring for the effect/adverse effect of drug absent or too infrequent 7.2.4. Monitoring may have occurred but is unavailable or not documented

Pharmacist-related factors		
Causes of DRPs according to The PCNE Classification V 6.2 (2010)	**Causes of DRPs according to the Aggregated System Category by Basger et al. (2015)**	
	5. Drug use process	
	5.8 Adequate information not provided or not understood or misunderstood or not followed	5.8.1. Adequate information about drug not provided 5.8.2. Incorrect information about drug provided 5.8.3. Adequate information about disease state management not provided or not understood or not followed
C6 Logistics	**6. Logistics**	
6.3. Dispensing error (wrong drug or dose dispensed)	6.2 Drug order incorrect, incomplete, poorly legible/illegible or discrepant (also known as transferring error)	6.2.3. The way in which information/directions were written caused the patient/carer to misuse the drug
	6.3 Error in drug selection	6.3.2. Pharmacist selects the wrong/expired drug from dispensary shelf
	7. Monitoring	
	7.1 Monitoring too frequent	7.1.1. Monitoring of disease state too frequent 7.1.2. Therapeutic drug monitoring too frequent 7.1.3. Monitoring for the effect/adverse effect of drug too frequent
	7.2 No or too infrequent monitoring	7.2.1. Monitoring of disease state absent or too infrequent 7.2.2. Therapeutic drug monitoring absent or too infrequent 7.2.3. Monitoring for the effect/adverse effect of drug absent or too infrequent 7.2.4. Monitoring may have occurred but is unavailable or not documented
PATIENT/CARER-RELATED FACTORS		
Causes of DRPs according to The PCNE Classification V6.2 (2010)	**Causes of DRPs according to the Aggregated System Category by Basger et al. (2015)**	
	3. Dose selection	
	3.6 Dosage instructions unclear, incomplete, or not understood by patient/carer	
C5 Drug use/administration process	**5. Drug use process**	
C5.1 Inappropriate timing of administration and/or dosing intervals	5.1 Inappropriate timing of administration and/or dosing intervals by patient/carer	

C5.2 Drug underused/underadministered (deliberately)	5.2 Drug underused/underadministered	5.2.1. The patient chose to take the wrong dose, which was lower than prescribed 5.2.2. The patient chose to take a drug on a "when required" basis rather than on a regular basis 5.2.3. The patient misunderstood the directions 5.2.4. The patient felt better or worse 5.2.5. The patient had a fear of adverse effects 5.2.6. The patient did not believe the drug was effective/believed the drug was toxic 5.2.7. The patient occasionally forgot to take the drug 5.2.8. The drug was underadministered by the carer
C5.3 Drug overused/overadministered (deliberately)	5.3 Drug overused/overadministered	5.3.1. The patient chose to take the wrong dose, which was higher than prescribed 5.3.2. The patient misunderstood the directions 5.3.3. The patient forgot they had already taken the drug 5.3.4. The drug was overadministered by carer
C5.4 Drug not taken/administered at all	5.4 Drug not taken/administered at all	5.4.1. The patient chose to discontinue a drug by choice or for an illogical or irrational reason 5.4.2. Patient forgot to take the drug
C5.5 Wrong drug taken/administered	5.5 Wrong drug selected, taken, or administered	
C5.6 Drug abused (unregulated overuse)	5.6 Drug abused	
C5.7 Patient unable to use drug/form as directed	5.7 Patient, carer, unable to use/does not use drug/form as directed	5.7.1. Patient uses drug incorrectly through difficulty or ignorance 5.7.2. Patient barriers are present
	5.8 Adequate information not provided or not understood or misunderstood or not followed	5.8.1. Adequate information about drug not provided 5.8.2. Incorrect information about drug provided 5.8.3. Adequate information about disease state management not provided or not understood or not followed 5.8.4. Incorrect information provided about disease state
	5.9 Patient uses or stores drug inappropriately	5.9.1. Inappropriate use/storage 5.9.2. Stockpiling
C7 Patient		
C7.1 Patient forgets to use/take drug		
C7.2 Patient uses unnecessary drug		
C7.3 Patient takes food that interacts		
C7.4 Patient stored drug inappropriately		

	6. Logistics	
	6.3 Error in drug selection	6.3.4. Patient takes someone else's drug
	7. Monitoring	
	7.4 Patient unable to attend/pay for monitoring	.
MEDICINE-RELATED FACTORS		
Causes of DRPs according to The PCNE Classification V6.2 (2010)	**Causes of DRPs according to the Aggregated System Category by Basger et al. (2015)**	
C1 Drug selection	**1. Drug selection**	
C1.1 Potentially inappropriate drugs	1.1 Inappropriate drug due to contraindication, ineffectiveness, regimen (regular rather than "when required") or safer alternative available	1.1.5. Drug is not effective for the indication being treated 1.1.6. Medical condition is refractory to drug
C1.3 Drug-drug/drug-food interactions	1.3 Inappropriate combination of drugs, or drugs and food, or drugs and alcohol	1.3.1. A drug interaction may cause/causes an undesirable reaction by increasing the therapeutic effect of one or both drugs 1.3.2. A drug interaction may cause/causes an undesirable reaction by decreasing the therapeutic effect of one or both drugs 1.3.3. A drug interaction may cause/causes a hypersensitivity reaction
C1.7 More cost-effective drugs available	1.5 More cost-effective drug available	
	8. Unexpected or adverse drug reaction or no obvious cause of DRP	
	8.1 An adverse drug reaction occurred	8.1.1. A drug causes an undesirable reaction that is not dose related 8.2.2. A drug causes an undesirable reaction at normal therapeutic dose 8.2 3. Allergic drug reaction
SYSTEM-RELATED FACTORS		
Both classification systems refer to a systems approach as they include causes of DRPs that may occur at every step of the medicine use process		

3 Factors associated with drug-related problems in the aged

Due to age-related body changes and increasing number of chronic diseases leading to polypharmacy, aged people are most vulnerable to DRPs requiring special attention with their pharmacotherapy (Mangoni and Jackson 2003, ELDesoky 2007, Hilmer et al. 2007a). Although DRP classifications described in the previous chapter are general, not age-specific, they are particularly valuable in geriatric pharmacotherapy in identifying DRPs and understanding their causes (Table 2). The model below (Figure 3) provides an illustration of key factors posing a risk to DRPs in the aged. The evidence for the model is derived from Table 2 and research described in more detail later in this chapter.

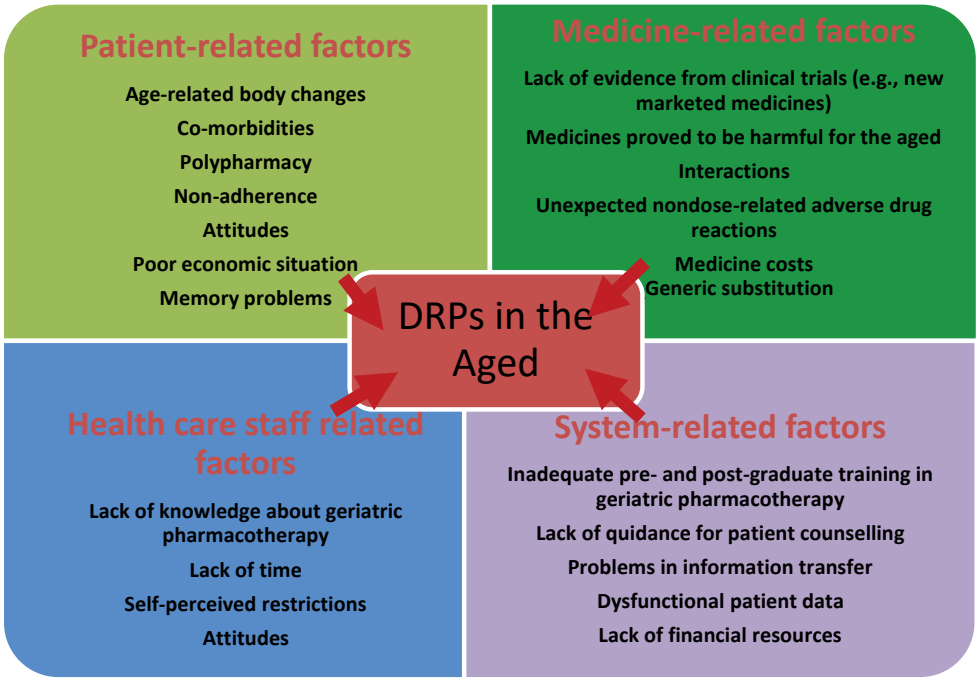

Figure 3 *Factors posing risks to DRPs in the aged (based on Table 2 and the articles focusing on DRPs in the aged that are discussed below)*

3.1 Patient-related factors

3.1.1 Age-related body changes and comorbidities leading to polypharmacy

Ageing is associated with several physiological changes that affect how medicines work in the body and thus, how medicines should be prescribed to older people (Table 3, Mangoni and Jackson 2003, ELDesoky 2007). Ageing also leads to impaired homeostasis and wide variability in drug response between individuals which makes medicine dosing and administration challenging (Hilmer et al. 2007a). The number of chronic diseases increases with advanced age leading to complex medications and polypharmacy (Jyrkkä et al. 2009a). Polypharmacy, in turn, increases risk of DRPs, such as adverse-drug reactions (ADRs). Fulton and Allen (2005) estimated that the risk of ADRs is 13% when using two medications, increasing up to 58% when using five medications. When using seven or more medications the ADR incidence risk increases to 82% (Prybus 2002). ADRs in the aged can be difficult to identify as they may be present as symptoms already prevalent in aged people e.g., dizzy spells, falls or confusion (Gaeta et al. 2002). Polypharmacy also increases the risk of having medicines classified as inappropriate for the aged (Fialova et al. 2005, Bell et al. 2013, Jirón et al. 2016).

Table 3. *Age-related changes and their influence on prescribing and/or medicine use in the aged (Mangoni and Jackson 2003, ELDesoky 2007, Hilmer et al. 2007a)*

<table>
<tr><th colspan="2">Physiological changes that can influence pharmacokinetics of medicines</th><th>Influence on prescribing and/or medicine use</th></tr>
<tr><td>General</td><td>1. Reduced total body mass
2. Changes in body composition
a) decrease in total body water => higher serum concentrations for hydrophilic medicines
b) increase in proportion of body fat => prolonged half time for lipophilic medicines</td><td rowspan="10">Increasing risk for adverse-drug reactions (ADRs)

Sensitivity to orthostatic episodes

Increasing need for careful monitoring of the patient's response to medicines

Need for dose adjustments (decrease)

Certain "high risk" medicines should be avoided when possible</td></tr>
<tr><td>Gastrointestinal tract</td><td>Reduced gastric emptying rate, gastric acid production, gut motility, gut blood flow</td></tr>
<tr><td>Circulation</td><td>Decreased cardiac output
Decreased plasma protein binding</td></tr>
<tr><td>Liver</td><td>Reduced liver mass and blood flow
=> reduced first pass metabolism
Reduced albumin synthesis
Alterations of hepatic enzymatic functions</td></tr>
<tr><td>Kidney</td><td>Reduced glomerular filtration rate
Reduced tubular function</td></tr>
<tr><td>Lung</td><td>Reduced vital capacity</td></tr>
<tr><td colspan="2">Physiological changes that can influence the pharmacodynamics of medicines</td></tr>
<tr><td colspan="2">Changes in 1. receptor density and/or affinity
2. signal transduction mechanism
Impairment of cellular response in affected organs</td></tr>
<tr><td colspan="2">Homeostasis</td></tr>
<tr><td colspan="2">Reduced homeostatic reserve</td></tr>
</table>

3.1.2 Patient-related factors associated with medication nonadherence

Physiological body changes are not the only patient-related factors posing risks to DRPs in aged medicine users. Behavioral aspects, such as negative attitudes towards medicines or alternatively non-drug treatments leading to nonadherence, also are important but quite often ignored factors leading to DRPs (Table 2, Figure 4). DRP classifications include several causes for DRPs that can be related to the way the patient selects or uses the medicines, gets the medicines administered, or are otherwise related to the patient's personality or behavior (Table 2, Figure 4, PCNE 2010, Basger et al. 2015). DRPs also may occur due to inadequate or wrong information and instructions, miscommunication and/or misunderstanding that can cause the patient to take the medicine incorrectly.

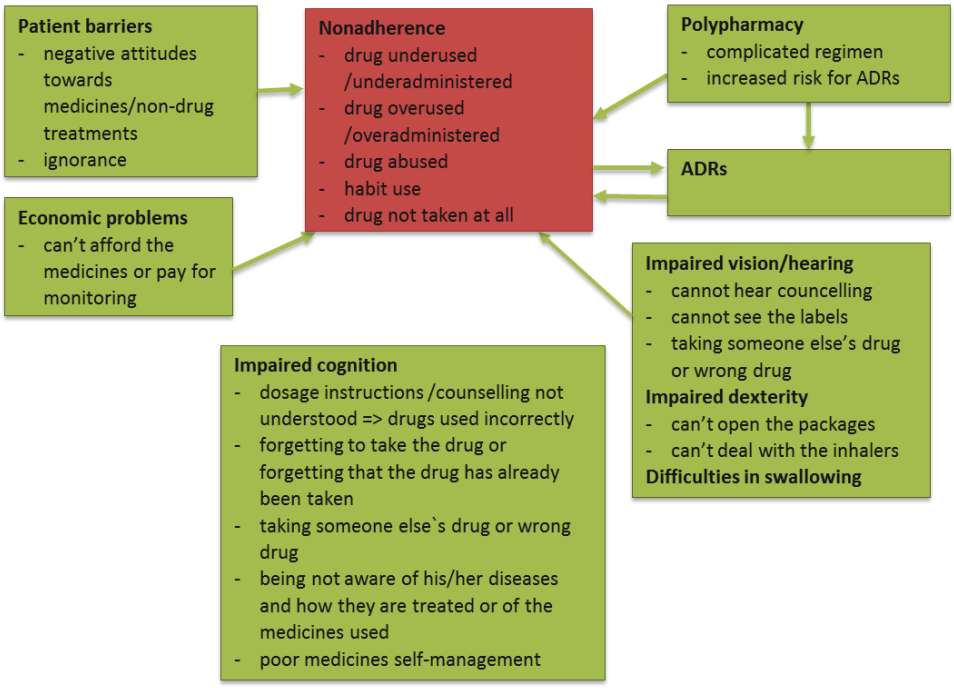

Figure 4 *Patient-related and medicine-related factors related to nonadherence posing risks to DRPs among aged medicine users. The model was constructed on the basis of studies by Fuller and Watson (2005), STAKES and ROHTO (2006), Dickinson et al. (2010), Doggrell (2010), PCNE (2010) and Basger et al. (2015)*

Medication adherence, defined as "the extent to which a person's behavior in taking medicines corresponds with agreed recommendations from a health care provider" (WHO 2003), is a key component in managing illnesses (Osterberg et al. 2005). Nonadherence, in its turn, has been associated to poorer health outcomes, residential care and hospital admissions and re-admissions, and thus, increased health care costs (Gurwitz et al. 2003,

Pirmohamed et al. 2004, Doggrell 2010). Nonadherence encompasses several aspects, such as (unintentional or intentional) underuse or overuse of medicines, habit use, abuse or neglected use of medicines (STAKES and ROHTO 2006, PCNE 2010, Basger et al. 2015). The likelihood of nonadherence is increased among the aged with many chronic illnesses and polypharmacy. It has been estimated that nonadherence rates among people aged ≥65 years vary from 40% to 75% (Doggrell 2010). Figure 4 summarizes key factors found to be related to medication nonadherence among the aged.

Reasons for nonadherence include factors related to the medicine (e.g., costs, number of medicines, adverse effects) and those related to the person (e.g., impaired cognition, impaired vision, depression, negative attitudes, poor economic situation) (Fuller and Watson 2005, Dickinson et al. 2010, Doggrell 2010, Figure 4). The study of Fuller and Watson (2005) identified that patient's mental state, attitudes towards and knowledge about medicines and visual impairment demonstrated a high risk to safe medicine self-management. Poor mental state, disinterested attitude towards medicine and living alone without help create a very high-risk situation irrespective of the number of prescribed medicines. Dickinson and colleagues (2010) investigated attitudes of older patients and their GPs to taking long-term antidepressant therapy. The study indicated that patients often echoed antipathy to non-drug treatment such as counselling. Related to habit use of medicines Dickinson and colleagues (2010) identified several barriers to discontinuation of antidepressants following four themes: 1) pessimism about the course and curability of chronic depression; 2) negative expectations and experiences related to aging; 3) discontinuation perceived by patients as a threat to stability; and 4) passive and active decisions to accept the continuing need for medication.

3.2 Medicine-related factors

Quite often the same evidence and therapeutic guidelines are applied to prescribing medicines to older adults as to "standard adults". This is due to the fact that there is a lack of evidence on the effects and safety of medicines in older adults (European Medicines Agency 2006 and 2015). This is the case for most licensed pharmaceutical products, not only for newly approved ones. The reason for the limited evidence is that aged people (especially those ≥80 years) continue to be under-enrolled in industry-sponsored pre approval drug studies or are excluded entirely from clinical trials although they are large medicine consumers for a number of chronic diseases (Van Spall et al. 2007, European Medicines Agency 2006 and 2015). This makes it difficult to generalize on the benefits and risks found in clinical trials for older patients who are typical users of those medicines. Also short trial durations and modest sample sizes are inadequate to fully predict actual clinical outcomes of newly marketed pharmaceutical products among the aged (European Medicines Agency 2006 and 2015, Van Spall et al. 2007, Avorn 2010). The demand for involving older adults in clinical trials is increasing (European Medicines Agency 2006 and 2015).

However, already today certain medicines and medicine groups are known to be harmful for the aged based on research and experience of experts in geriatric care and

pharmacotherapy. Based on literature reviews and these expert opinions e.g., benzodiazepines, strong anticholinergics and antipsychotics are listed as potentially inappropriate medicines (PIMs) for the aged, and should be avoided where possible (AGS 2015, Finnish Medicines Agency 2015a). Since 1991, several criteria listing medicines potentially inappropriate for the aged have been developed in order to manage potential risks caused by these medicines (Beers et al. 1991, Fick et al. 2003, AGS 2015, Finnish Medicines Agency 2015a). However, although not being recognized as PIMs all medicines can cause undesirable reactions (e.g., allergic reactions) that are not dose-related and may occur at a normal therapeutic dose.

Generic substitution, i.e., once a patent has expired, a medicine is sold under a generic name (International Nonproprietary Name (INNs)) as a substitute for the original brand-name medicine, is a risk factor for medication errors (Schwab et al. 2002, Håkonsen et al. 2011, Lobo et al. 2013). Using both trade and generic names of medicines may lead to confusion and subsequently to overdosing and also may influence in adherence (Schwab et al. 2002, Colombo et al. 2016).

3.3 Health care staff related factors

3.3.1 Prescriber

Several factors relating to prescribing may cause DRPs among the aged (Table 2, PCNE 2010, Basger et al. 2015). Inappropriate drug selection e.g., selection of "high risk drugs", contraindicated drugs, inappropriate combination of drugs, or drugs and food, or drugs and alcohol, may represent causes for DRPs. Some indications may not be treated and via versa some medicines may be prescribed without indication. Drug form, treatment duration or dose selection may be inappropriate, also issues related to logistics (e.g., a drug order does not meet legislative requirements) may represent risk to DRPs.

Although several prevalence studies in several countries indicate that inappropriate prescribing among the aged is common both in outpatient and inpatient care (Panesar et al. 2015), less attention has been paid to why it happens and how it can be prevented. A recent meta-synthesis (i.e., a qualitative synthesis) of Cullinan and colleagues (2014) offers a novel approach to understanding why it happens from the prescriber's point of view. The meta-synthesis base on a literature search of English language studies that use qualitative methods and explore some area of potentially inappropriate prescribing among patients 65 years and over (Cullinan et al. 2014). A systematic search from PubMed, Embase, CINAHL and Web of Knowledge databases up to the end of April 2013 (no start day was specified) produced 7 articles (Damestoy et al. 1999, Spinewine et al. 2005, Cook et al. 2007, Agarwal et al. 2008, Wood-Mitchell et al. 2008, Dickinson et al. 2010, Spitz et al. 2011). Most of those articles (71%) handled prescribing of CNS medications i.e., psychotropics, benzodiazepines, antidepressants and opioids (Damestoy et al. 1999, Cook et al. 2007, Wood-Mitchell et al. 2008, Dickinson et al. 2010, Spitz et al. 2011). Results of the meta-

synthesis indicated that physicians often have self-perceived restrictions leading to a sense of powerlessness to prescribe appropriately (Cullinan et al. 2014). The study found four key concepts being causal factors in inappropriate prescribing: 1) the need to please the patient; 2) a feeling of being forced to prescribe; 3) tension between prescribing experience and prescribing guidelines and 4) prescriber fear. These thematic concepts are described in more detail below.

3.3.1.1 The need to please the patient

Although a patient-centered approach to pharmacotherapy has been highlighted, at times, the patient may have too much of a deciding role in his/her therapy. This may complicate the physician's decision making and prevent actions that would objectively be best for the patient (Cullinan et al. 2014). Cook et al. (2007) explored practicing primary care physicians' attitudes to prescribing benzodiazepines for older adults. None of the physicians considered benzodiazepines use among the aged to be a priority clinical or public health problem. They saw no cases of addiction in their aged patients and focused a little recognition to adverse effects other than addiction, which they saw as the main concern of benzodiazepine use and discontinuation. They thought that the continuation of benzodiazepine use is compassionate and discontinuation harsh. They found it quicker and easier to prescribe what the patient wants than spend time persuading patients that a different approach to managing insomnia or anxiety would be preferable. They also expressed pessimism in successful tapering or discontinuation in aged patients with long-term use of benzodiazepines and referred to prior failed attempts. Dickinson et al. (2010) found that both GPs and their patients found discontinuation of long-term use of antidepressants as a threat to stability; they did not want to "rock the boat". The possibility of the patient's switching to another physician was also identified as a reason for inappropriate prescribing (Damestoy et al. 1999, Cook et al. 2007). Damestoy and colleagues (1999) described how patients, previously described as fragile and vulnerable, became demanding and difficult when their use of anxiolytics was questioned.

3.3.1.2 Feeling forced to prescribe

In addition to the need to please the patient there also were other situations, where the physicians felt that they were forced to prescribe, or not prescribe although they realized it was not appropriate (Cullinan et al. 2014). Wood-Mitchell et al. (2008) found that psychiatrists (working in inpatient clinics and in community-care settings) felt pressured to prescribe psychotropics for behavioral and psychological symptoms of dementia due to resource issues (e.g., differences in the level of care between care homes) and lack of availability of alternative treatments. Also the study of Dickinson and colleagues (2010) found that one frequently cited reason for favouring antidepressants by GPs working in primary care trusts was inadequacy or unavailability of alternative treatments. Some physicians realized an inappropriate use of certain medicines to be a public health problem

but they felt it was beyond the scope of an individual physician (Damestoy et al. 1999, Cook et al. 2006). In a study of Agarwal and colleagues (2008) GPs described situations where their experience of the lack of knowledge in particular nursing homes or less-than ideal care situations, hindered them from considering insulin treatment.

3.3.1.3 Experience vs. guidelines

According to the meta-synthesis of Cullinan et al. (2014) the prescribers were aware of the potentially inappropriate nature of some of their prescribing and mostly were aware of the treatment guidelines and agreed with them. However, they felt that it was difficult to implement the guidelines in practice and the end result was reversion to previous practices which they were familiar with. Lack of evidence supporting some guidelines also influenced the prescribers in favour of their own experiences (Wood-Mitchell et al. 2008). As the physicians did not often see the adverse effects there was little concern about those (Cook et al. 2008, Dickinson et al. 2010).

3.3.1.4 Prescriber fear

Feeling a sense of fear in prescribing to older patients due to frailty and co-morbidities (fear of causing harm) were reported by physicians (Spinewine et al. 2005, Argwall et al. 2008). In a study of Spitz et al. (2011) the physicians described the fear of prescribing opioids for older patients because of the worry regarding several adverse effects. The physicians also reported that they did not want to stop certain medications because of the fear of disrupting patients' clinical stability (Dickinson et al. 2010). The physicians also reported a fear of offending other doctors, including specialists and GPs (Spinewine et al. 2005). E.g., when the physician noticed something potentially inappropriate, but it was prescribed by a specialist, it was not likely they intervened, or the patient transfer information between levels of care could be limited by fear of offending the prescribed physician with comments of inappropriate prescribing.

3.3.1.5 Interventions to promote appropriate prescribing

Results of the meta-synthesis indicate that methods for empowering physicians to prescribe appropriately should be developed (Cullinan et al. 2014). Educational interventions, such as pre- and postgraduate education about geriatric pharmacotherapy, improving "non-technical skills" such as communication skills, team-working, leadership and risk-managing skills could also be possible methods. At the systems level ways to improve communication between levels of care should be further developed and resources for geriatric care should be increased.

3.3.2 Nurses and pharmacists

Errors in the drug use process (administration, dosing), in logistics (administering a drug from the wrong patient's drug chart), inappropriate monitoring or incorrect or inadequate patient counselling are among factors that may cause DRPs related to both nurses and pharmacists (Table 2, PCNE 2010, Basger et al. 2015). In addition to the above mentioned, dispensing errors may cause DRPs related to pharmacists.

3.4 System-related factors

Several of the above mentioned risk factors could be managed by improving the health care system, which is a challenge that requires attention in national level and should be priority in health policy making (Airaksinen et al. 2012). Competence and curriculum development, improving data systems in and between health care units, improving conditions under which people work (e.g., adequate guidance on processes) and assuring accessibility and quality of medicines information both for the health care staff and the patients are among the important issues that should be focused on related to a systems approach to medication safety.

3.4.1 Competence and curriculum development

3.4.1.1 Geriatric pharmacotherapy

Inappropriate prescribing (e.g., selection of wrong or inappropriate medicine, errors in dosage regimen), administration errors, inadequate or incorrect patient counselling and inadequate follow-up evaluation may result from health care professionals' lack of knowledge in geriatric pharmacotherapy. Several studies indicate that there are deficiencies in geriatric pharmacotherapy skills among health care professionals (Kivelä 2006, Avorn 2010, Cullinan et al. 2014). Thus, curriculum redesign and adequate continuing education, focusing more on geriatric pharmacotherapy, should be key components in improving educational programs for all health care professionals (physicians, nurses, pharmacists).

3.4.1.2 Interprofessional co-operation

Inadequate or incorrect information transfer between different health care professionals may also lead to medication errors. Information may also be misunderstood. In order to learn working together and discussing "the same language" interprofessional co-operation should be emphasized and trained already during basic education (WHO 2010). In practice, actions aiming to influence attitudes and traditional norms within health care institutions should be done in order to support interprofessional co-operation (Kallio 2014).

3.4.2 Data systems

Errors in information transfer when patients are transferred between different levels of care (e.g., from hospital to long-term care) or between different health care units may cause DRPs (Crotty et al. 2004, PCNE 2010, Basger et al. 2015). Lack of uniform patient data registering practices by all health care professionals may also cause errors. Thus, several demands concerning the data systems also exist. Compatible data systems between different health care units, in order to assure continuous and reliable information transfer, should be guaranteed (Ministry of Social Affairs and Health 2011a). Health care professionals' technical skills to ensure reliable use of the software programs should be assured. Systems supporting rational prescribing practices should be further developed and introduced. Tools developed to improve medication safety should be actively distributed and further developed for use throughout the whole pharmacotherapy process and for all professionals dealing with the pharmacotherapy of the aged.

3.4.3 Guidance on processes within health care institutions

Health care institutions should be supported to develop plans and procedures to improve medication safety (Ministry of Social Affairs and Health 2011a). Disease specific care pathways, unit based and individual pharmacotherapy plans are among the most important actions as well as naming a person in charge for each patient.

3.4.4 Medicines information and empowerment

Inadequate and/or unreliable medicines information provided to health care professionals or to the patients may result in pharmacotherapy risks (Finnish Medicines Agency 2012, Hämeen-Anttila et al. 2012 and 2013). Especially, in regard to the aged medicine users actions focusing on increasing readability and understandability of the information should be emphasized. Patient empowerment and involvement in their own care have been focused on as key components in improving medication safety (Ministry of Social Affairs and Health 2011a). Not only the patients but also the health care professionals should be empowered to appropriate pharmacotherapy of the aged (Cullinan et al. 2014).

4 Risk management in geriatric pharmacotherapy

4.1 Systems approach to risk management

A landmark article on general principles of risk management was published by James Reason in 2000. Reason's (2000) principle of human error changed the ideology in risk management from an individual to a systems level. Reason viewed the problem of human error in two ways "persons approach" and "systems approach". The persons approach focuses on individual errors, such as forgetfulness or inattention. The systems approach concentrates on the conditions under which people work, and tries to build defenses to avert errors or mitigate their effects. Reason (2000) introduced the "Swiss Cheese" model to illustrate the idea of managing the risks of organizational accidents (Figure 5). This systems approach encompasses successive layers of defence, barriers and safeguards in the process in order to prevent single individuals making mistakes.

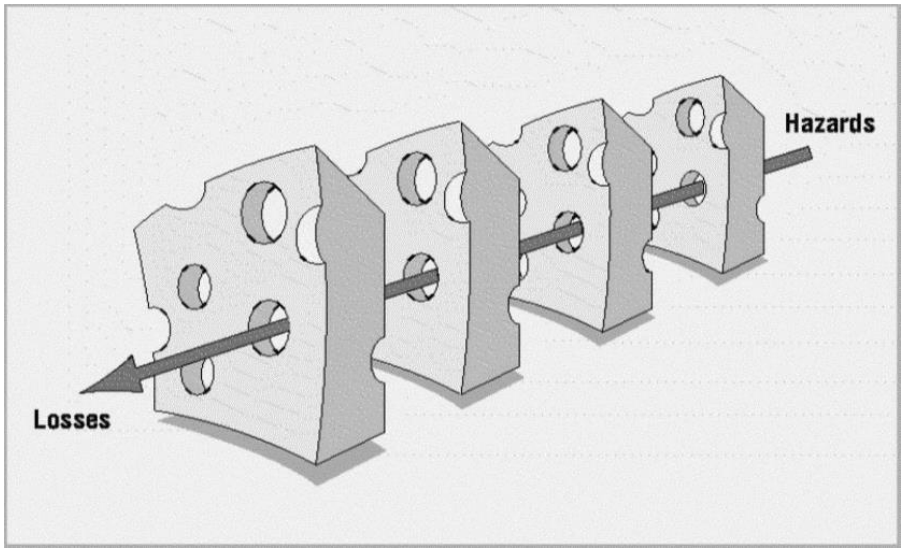

Figure 5 *Human error - The Swiss Cheese Model illustrating risk management from systems approach (Reason 2000)*

4.1.1 Extending the Swiss Cheese Model to managing risks in pharmacotherapy

The "Swiss Cheese" model has been widely used to illustrate the systems approach to patient and medication safety (Council of Europe 2006a and b, WHO 2011). Medication errors may be named as causes of DRPs (PCNE 2010) or, medication errors can be the cause

of risks to DRPs (Council of Europe 2006a). Among the most discussed preventitive actions for medication errors and consequently DRPs have been different types of medication reviews (Leikola 2012, Bulajeva et al. 2014, Kiiski et al. 2016), medication counselling, multidose dispensing/automated dose dispensing (Sinnemäki et al. 2013 and 2014), manual and electronic risk assessment tools, and other collaborative and coordinated practices involving pharmacists as part of the team (Kivelä 2006, Ministry of Social Affairs and Health 2007, Finnish Medicines Agency 2016). Figure 6 shows a modification of Reason's (2000) Swiss Cheese Model that illustrates how interprofessional collaboration can be coordinated to assist in risk management of pharmacotherapies at different levels of care involving patients and healthcare providers with the available skills and tools that each of them have (Modified from Chen et al. 2006).

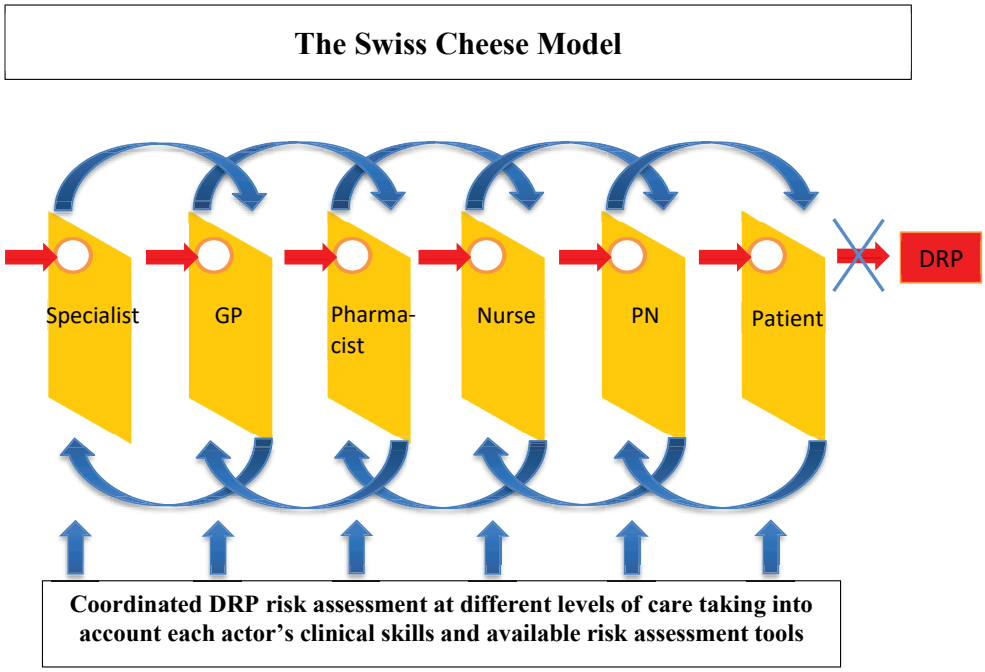

Figure 6 *Modification of Reason's (2000) Swiss Cheese Model to illustrate interprofessional approach to DRP risk management in pharmacotherapy (Modified from Chen et al. 2006) (DRP=drug-related problem, GP=general practitioner, PN=practical nurse)*

Another modification of Reason's Swiss Cheese Model illustrates how collaborative medication reviews can be used as a preventive action for medication errors (Figure 7, Chen et al. 2006). In that model, the medication process covers also the manufacturer and regulatory authority which assures that pharmaceutical products are effective and safe. Medication reviews are planned to cover the medication use part of the process, including, e.g., prescribing, dispensing and monitoring.

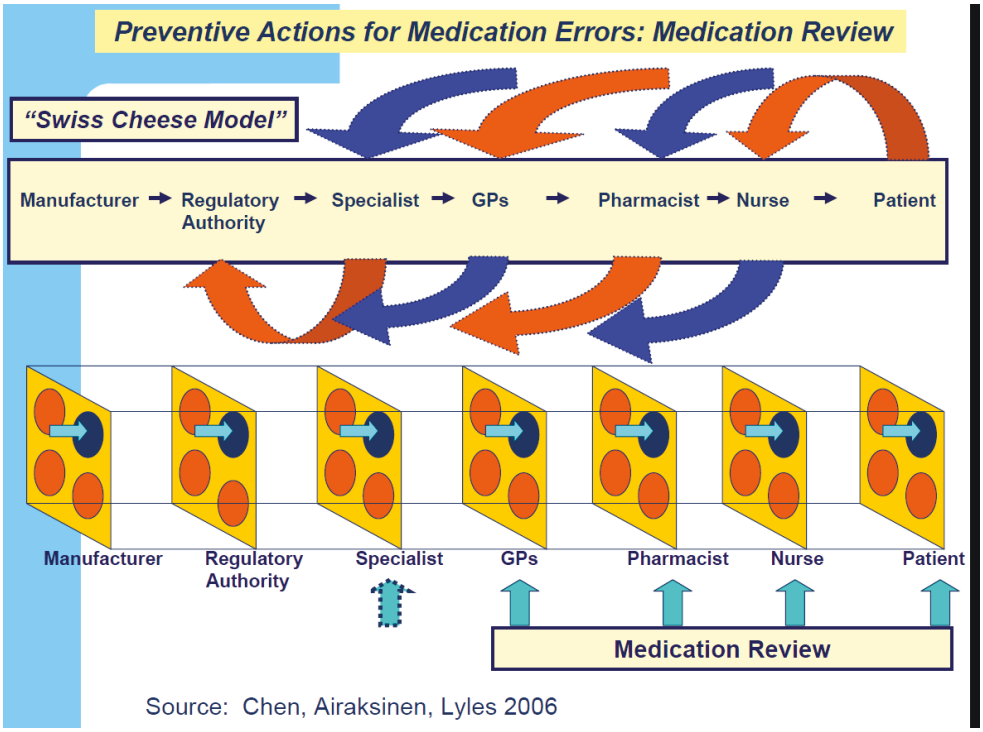

Figure 7 *Another modification of Reason's (2000) Swiss Cheese Model to illustrate how collaborative medication reviews can be used as a preventive action to medication errors in healthcare (Chen et al. 2006) (GP=general practitioner)*

4.1.2 Hepler and Strand's pharmaceutical care philosophy in operationalizing Reason's human error theory in medication risk management

Hepler and Strand's pharmaceutical care philosophy (Hepler and Strand 1990) assists in operationalizing Reason's (2000) general human error theory in medication risk management. As Figures 6 and 7 show, DRPs and collaborative medication reviews, concepts introduced by Hepler and Strand in medication management, fit well to the idea of medication risk management providing concrete tools for identifying, solving and preventing DRPs. Other medication-specific procedures and tools can similarly be regarded as system-based preventive actions to improve medication safety. The philosophy of pharmaceutical care and efforts to implement it in different countries throughout the world since 1990s has brought community and hospital pharmacists more involved in medication risk management in healthcare (Berenguer et al. 2004, van Mil et al. 2004b, Besangon 2010, Harris et al. 2014).

4.2 DRP risk management tools

Medication reviews at different levels have been recognized as fundamental in medication risk management (National Health Service Act 2006, APhA and NACDS Foundation 2008, Pharmaceutical Society of Australia 2011a and b, Leikola et al. 2012a, PCNE 2016a). This has led to the need to develop tools for identifying risk patients needing medication reviews. The first screening tool for medication risks was developed by Koecheler et al. in 1989. The tool consisted of six medication risk predicting indicators. It was designed for use by pharmacists, when reviewing patient charts in ambulatory care clinics, to screen patients that may have problems in their medication (Koecheler et al. 1989).

Later, realizing the fact that due to pharmacokinetic and pharmacodynamic alterations and multimorbidity leading to polypharmacy, aged people may, in terms of pharmacology, be considered as "a special population" needing geriatric specific screening tools (Barenholz Levy 2003, Johnson et al. 2005). In addition to different screening tools, the need for tools to identify potentially inappropriate prescribing among the aged became evident. The first prescribing guidelines were published by Dr. Mark Beers MD, a geriatrician from the US who developed prescribing guidelines for nursing homes, the so called Beers criteria (Beers et al. 1991). The DRP classifications described in Chapter 2 are useful in documenting DRPs and their causes identified during medication reviews. Figure 8 illustrates how different risk management tools can be integrated in a medication review process targeted at the aged. Essential tools in risk management in geriatric pharmacotherapy are discussed in this Chapter.

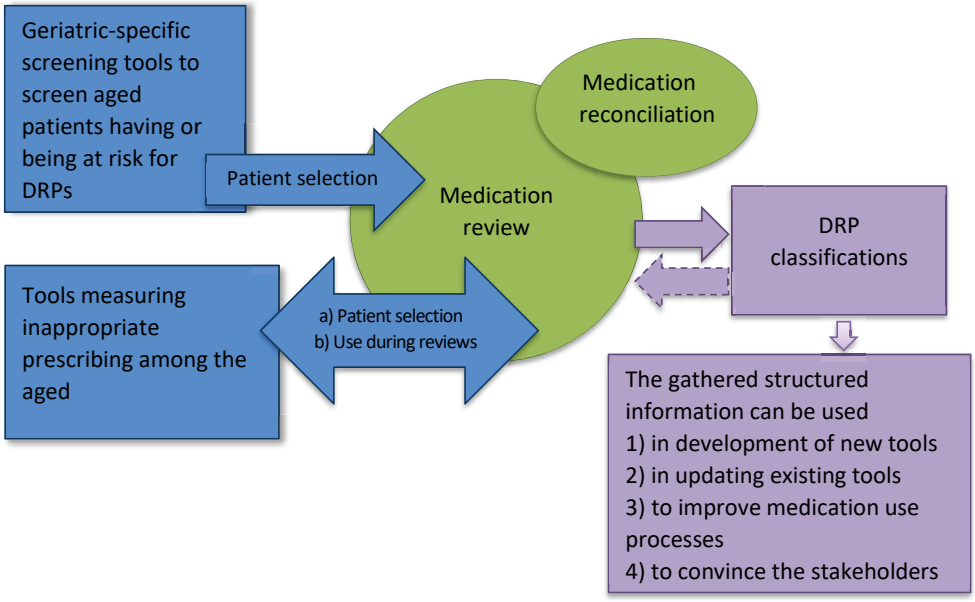

Figure 8 *Illustration of how different kinds of risk management tools can be integrated in a medication review process*

4.2.1 Medication review procedures

In order to ensure safe and rational medication use several medication review procedures have been developed worldwide over the last decades. The first procedures originate from the US, where prospective Drug Utilization Reviews (pDUR) were mandated since 1993 after the passage of the Omnibus Budget Reconciliation Act of 1990 (OBRA '90) (Lyles et al. 2001, Fulda et al. 2004, Bulajeva et al. 2014). DURs have evolved into Medication Therapy Management (MTM) procedures in the US, the development being coordinated by AphA and National Association of Chain Drug Stores Foundation (APhA and NACDS Foundation 2008). In addition to the US, Australia and the United Kingdom have been forerunners in the development of medication review procedures, those also being the first countries in incorporating the medication review services into primary outpatient care (Lyles et al. 2001, Fulda et al. 2004, Leikola 2012). According to the online survey in 2010, medication review procedures are becoming common also in healthcare throughout Europe (Bulajeva et al. 2014). Almost two thirds (64%; 16/25) of the European countries which responded in 2010 indicated having at least one type of medication review procedure in their country.

Definitions of the term "medication review" differ as well as the medication review procedures created in different countries (Clyne et al. 2008, APhA and NACDS Foundation 2008, Leikola 2012, Bulajeva et al. 2014, AACP 2016, PCNE 2016a, Table 4). Medication reviews can be retrospective or prospective (Lyles et al. 2001, Fulda et al. 2004, Clyne et al. 2008, Figure 9). Prospective reviews like prospective DUR (pDUR) in the US assess the appropriateness of pharmacotherapy at patient level during dispensing e.g., drug-drug interactions, drug-disease contraindications (Fulda et al. 2004). Retrospective reviews occur after the medicines have been dispensed and the reviews take into account the patient's whole medical history and depending on the review's comprehensiveness also system related factors (Clyne et al. 2008, APhA and NACDS Foundation 2008, Leikola 2012, AACP 2016, PCNE 2016a). In collaborative medication review procedures the pharmacist's role is essential in identifying DRPs and solving them jointly with physicians, nurses, patients and others involved in the care of each individual patient (Leikola 2012, AACP 2016).

The medication review procedures may also differ in the setting (hospital vs primary care) where they are conducted. E.g., in Australia medication review procedures have been developed both for inpatient settings (Residential Medication Management Review (RMMR)) and for community-dwellers (Home Medicines Review (HMR), also known as Domiciliary Medication Management Review (DMMR)) (Pharmaceutical Society of Australia 2011a and b, AACP 2016). The procedures may differ also in comprehensiveness (prescription review, adherence and compliance review, clinical medication review) and in the levels of multiprofessional collaboration (Clyne et al. 2008, APhA and NACDS Foundation 2008, Leikola 2012, Bulajeva et al. 2014, AACP 2016) RMMR and HMR (DMMR) in Australia are comprehensive assessments of patient's medication conducted by pharmacists in collaboration with the GP (Pharmaceutical Society of Australia 2011a and b, AACP 2016), while Medication Use Review (MUR) in the UK can be classified as an adherence and compliance review where the pharmacist contacts the physician if needed

(Clyne et al. 2008). The medication therapy review (MTR) procedure in US is flexible allowing comprehensive or targeted reviews depending on the needs of the patient (APhA and NACDS Foundation 2008). The procedures may also be developed for special patient groups, e.g., the Finnish CMR procedure is especially designed for geriatric patients (Leikola 2012). In addition to the above mentioned differences the study of Bulajeva et al. (2014) reported differences in access to clinical patient information, documentation forms available, quality control and competence requirements (Bulajeva et al. 2014). The procedures may be local or national.

Table 4. *Examples of different definitions of medication review procedures*

Country/Area	Review	Definition
Europe	PCNE	A structured evaluation of patient's medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions (PCNE 2016a)
Finland	CMR	A medication review procedure applied nationally in Finland and requiring accreditation training for pharmacists conducting it. The procedure is based on collaboration between pharmacists 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 (Leikola 2012)
United Kingdom	MUR	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 (Clyne et al. 2008)
Australia	HMR (DMMR)	A Home Medicines Review (HMR) (also known as Domiciliary Medication Management Review (DMMR)) involves the patient, their general practitioner (GP), an accredited pharmacist and regular community pharmacy. In some cases, other relevant members of the healthcare team, such as nurses in community practice or carers, are included. The pharmacist visits the patient at their home, reviews their medicine routine and provides their GP with a report. The GP and patient then agree on a medicine management plan (AACP 2016)
	RMMR	A Residential Medication Management Review (RMMR) is a service provided to a permanent resident of an Australian Government funded aged care facility (ACF). This includes those in flexible care arrangements (transitional care facilities), who are not eligible for a Home Medicines Review (HMR) (AACP 2016)
United States	MTM	The medication therapy review (MTM) is a systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them (APhA and NACDS Foundation 2008)

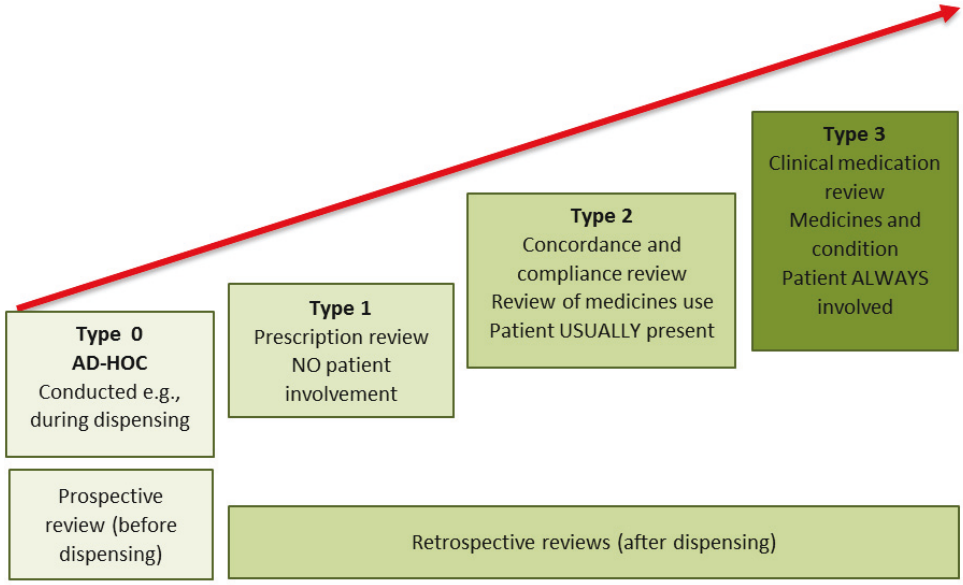

Figure 9 *Different types of medication reviews constructed on the basis of Lyles et al. 2001, Fulda et al. 2004 and Clyne et al. 2008*

4.2.1.1 Implementing medication reviews in health care systems and setting up criteria for patient selection

Medicines are used in different ways in different care pathways and in different care settings. Therefore, identification of the points of care where medication reviews are likely to be beneficial is crucial. Likewise, the comprehensiveness of the procedure needs careful consideration in the selection phase. The most time consuming and expensive of the procedures are comprehensive medication reviews. Thus, patients undergoing this type of procedure need to be carefully selected. In countries where medication reviews are integrated in the health system (e.g., Australia: HMR (DMMR), RMMR; United States: MTM; , The United Kingdom: MUR) inclusion criteria for patient selection have been developed (APhA 2008, Pharmaceutical Society of Australia 2011a and b, Royal Pharmaceutical Society 2016, Table 5). The CMR procedure developed in Finland recommends for the patient selection that there is a potential DRP or risk for DRP identified by the patient, nurse or pharmacist and the physician has confirmed that the patient may benefit from CMR in order to recognize and solve DRPs (Leikola 2012). Further research is still needed in setting up evidence-based criteria for patient selection for medication reviews and deciding the comprehensiveness of the review required to detect and solve DRPs.

Table 5. *Target groups for medication review services in Australia, United Kingdom and United States*

<table>
<tr><th colspan="2">Australia</th><th>United Kingdom</th><th>United States</th></tr>
<tr><th>HMR (DMMR)</th><th>RMMR</th><th>MUR</th><th>MTM</th></tr>
<tr><td>Currently taking five or more regular medications</td><td rowspan="2">New residents on admission into a Residential Aged Care facility (RACF)</td><td rowspan="3">Patients taking any of the following medicines: NSAIDs, anticoagulants (including low molecular weight heparin), antiplatelets, diuretics</td><td>Patient has experienced a transition of care, and his or her regimen has changed</td></tr>
<tr><td rowspan="2">Taking more than 12 doses of medication per day</td><td>Patient is receiving care from more than one prescriber</td></tr>
<tr><td rowspan="2">Existing residents on an 'as required' basis, where in the opinion of the resident's medical practitioner, it is required because of a significant change in medical condition or medication regimen</td><td>Patient is taking five or more chronic medications (including prescription and nonprescription medications, herbal products, and other dietary supplements)</td></tr>
<tr><td>Significant changes made to medication treatment regimen in the last 3 months</td><td rowspan="2">Patients recently discharged from hospital who have had a change in medicines during their hospital stay</td><td rowspan="2">Patient has at least one chronic disease or chronic health condition (e.g., heart failure, diabetes, hypertension, hyperlipidemia, asthma, osteoporosis, depression, osteoarthritis, chronic obstructive pulmonary disease)</td></tr>
<tr><td>Symptoms suggestive of an adverse drug reaction</td></tr>
<tr><td>Sub-optimal response to treatment with medicines</td><td rowspan="8">Patients with a respiratory disease taking the following medicines for asthma or COPD
- Adrenoceptor agonists
- Antimuscarinic bronchodilators
- Theophylline
- Compound bronchodilator preparations
- Corticosteroids
- Cromoglicate and related therapy, leukotriene receptor antagonists and phosphodiesterase type-4s</td><td>Patient has laboratory values outside the normal range that could be caused by or may be improved with medication therapy</td></tr>
<tr><td>Medication with a narrow therapeutic index or medications requiring therapeutic monitoring</td><td rowspan="2">Patient has demonstrated nonadherence (including underuse and overuse) to a medication regimen</td></tr>
<tr><td rowspan="2">Patients having difficulty managing their own medicines because of literacy or language difficulties, dexterity problems or impaired sight, confusion/ dementia or other cognitive difficulties</td></tr>
<tr><td>Patient has limited health literacy or cultural differences, requiring special communication strategies to optimize care</td></tr>
<tr><td>Patient wants or needs to reduce out-of-pocket medication costs</td></tr>
<tr><td rowspan="2">Patients attending a number of different doctors, both general practitioners and specialists</td><td rowspan="2">Patient has experienced a loss or significant change in health plan benefit or insurance coverage</td></tr>
<tr><td rowspan="2">Recent discharge from a facility/ hospital (in the last four weeks)</td></tr>
<tr><td>Patient has recently experienced an adverse event (medication or non-medication-related) while receiving care</td></tr>
<tr><td colspan="2"></td><td>Patient is taking high-risk medication(s), including narrow therapeutic index drugs (e.g., warfarin, , methotrexate)</td></tr>
<tr><td colspan="2"></td><td></td><td>Patient self-identifies and presents with perceived need for MTM services</td></tr>
<tr><td colspan="4">COPD=Chronic Obstructive Pulmonary Disease, DMMR=Domiciliary Medication Management Review, HMR=Home Medicines Review, MUR=Medication Use Review, MTM=Medication Therapy Management, NSAID=Nonsteroidal Anti-inflammatory Drug, RMMR=Residential Medication Management Review</td></tr>
</table>

4.2.2 Medication reconciliation

Poor communication of medical information when patients are transferred between different levels and points of care may cause medication errors resulting in adverse drug events (ADEs) (Crotty et al. 2004, Gleason et al. 2010). Medication reconciliation (MR) is a process of identifying the most accurate list of the medicines a patient is taking (name, dosage, frequency, and route) (Council of Europe 2006a). Reconciliation involves comparing the patient's current medication list with the physician's admission, transfer, and/or discharge orders. Use of this list promotes continuity of treatment between different levels and points of care. According to a recent systematic literature review, MR in hospitals, community settings and residential age care facilities has the potential to identify several medication discrepancies and reduce potential harm (Lehnbom et al. 2014). However, there is limited evidence that MR significantly improves clinical outcomes such as reductions in hospital admissions.

4.2.3 Inventory of Tools designed to screen patients at risk for or having DRPs

As the aim of this thesis was to develop and validate a DRP risk assessment tool for use by practical nurses taking care of home-dwelling clients ≥65 years, an inventory of existing DRP risk assessment tools was conducted. Although this Chapter focuses especially on geriatric-specific screening tools designed to be used in outpatient care, also the other tools found in the search are briefly discussed. The following aspects of the geriatric-specific tools are studied: target group, contents of the tools, in which circumstances and by whom the tools are intended to be administered.

Of the 11 screening tools found (Koecheler et al. 1998, Isaksen et al. 1999, Barenholz Levy 2003, Fuller and Watson 2005, Johnson et al. 2005, Langford et al. 2006, Pit et al. 2007, Hedström et al. 2009, Barnett et al. 2011, Gushdal et al. 2011, Pammett et al. 2015) six are geriatric-specific (Barenholz Levy 2003, Fuller and Watson 2005, Johnson et al. 2005, Pit et al. 2007, Hedström et al. 2009, Gushdal et al. 2011, Table 6). The first screening tools were developed in the United States (Koecheler et al. 1989, Isaksen et al. 1999, Barenholz-Levy 2003), followed by a tool developed in Canada several years later (Langford et al. 2006). Of the found 11 screening tools six (55%) are based mainly or partly on Koechelers' six risk predicting indicators (Figure 10). Generally, these tools are easy and fast to use, and thus, are suitable to be used by various health care professionals or by patients themselves in several circumstances.

Table 6. *Geriatric-specific screening tools developed for use in outpatient care (n=6)*

Risk predicting items included in the geriatric-specific screening tools		Barenholz Levy 2003 US	Fuller and Watson 2005 UK	Johnson et al. 2005 Australia	Pit et al. 2008 Australia	Hedström et al. 2009 Sweden	Gusdal et al. 2011 Sweden
		Target group					
		Ambulatory patients aged ≥ 65 years	Home-dwelling older people living alone	People aged ≥ 65 years within community-based nursing caseloads	Community-dwelling aged ≥ 65 years	People aged ≥ 65 years in nursing homes and outpatient settings	Home-care patients ≥ 75 years
		Who administers the tool					
		Patients	Various health care professionals	Public health nurses	Patients	Nurse, proxy, patient	District nurse
Risk predicting items related to medicine use	Number of medicines	x	x		x		x
	Twelve or more medication doses/day	x					
	Medication regimen changed four or more times during the past 12 months	x		x	x		
	Starting a new medicine in the last 4 weeks				x		
	Using certain medicines				x[2)]		
	Presence of medicines that require therapeutic monitoring	x					
	Have been taking medicines for more than six months				x		
	Taking medicines for more than 3 medical problems	x					
	Sharing medicines with someone else				x		
	Have the medicines been checked by the physician in the past 12 months				x		
	Prescriptions are filled at more than one pharmacy	x					
	Someone else than the patient themself brings medicines to the patient	x					

ADR	Symptoms suggestive of adverse drug reactions				x[3)]	x[4)]	
Health, health care setting and care taking physicians	More than one physician involved in patient´s regular care	x		x	x		
	The patient has changed his/her general practitioner in past 3 months				x		
	More than three concurrent disease states present				x		
	Mental state		x				
	Hearing, vision		x				
	Physical condition		x				
	Self-rated poor health				x		
	The patient has been in hospital, hostel or nursing home in the past month				x		
Adherence	Compliance issues	x		x[1)]	x		
	Attitudes towards medication		x				x
	Patient's awareness of his/her medicines (what they are used for etc…)	x					
Demographics	Social circumstances		x		x		
	Caregiver available			x			

ADR=Adverse drug reaction

[1)] Sometimes forgetting to take medications

[2)] Medicines that help to sleep, medicines for nerves, stress, anxiety or depression, medicines that the physician does not know about

[3)] Patient's symptoms during the last month: trouble in sleeping, felt drowsy or dizzy, felt nauseous, stomach problems, skin rash/itch, leaked urine, constipation (Pit et al. 2007)

[4)] Patient's symptoms during the last two weeks: dizzy/unsteady/high risk of falls, tired/exhausted, poor sleep pattern/nightmares, abdominal pain/chest pain, headache, low mood, worried/anxious, irritable, forgetful, poor appetite, dry mouth, nausea/vomiting, diarrhoea, constipation, palpitation (rapid/irregular heartbeat), swollen legs/ankles, short of breath, frequent urination/incontinent of urine, itching/rash, other symptoms, which the patient has experienced during the past two weeks (e.g., pain) (Landstinget I Uppsala Län, 2014a, b and c)

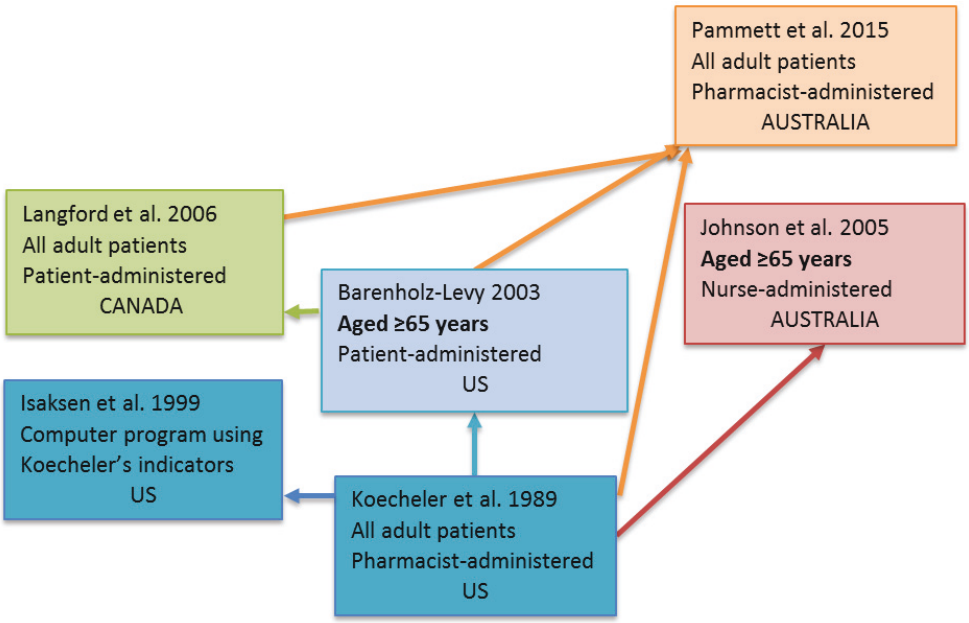

Figure 10 *Screening tools derived from Koecheler's six indicators*

4.2.3.1 Koecheler's six risk predicting indicators

To my knowledge, the first screening tool developed to identify patients at risk for, or having DRPs was published by Koecheler and colleagues in 1989 (Koecheler et al. 1989) (Figure 10). The tool was general, not age-specific and designed to be used by pharmacists when reviewing patients' medication charts in ambulatory care clinics. It encompasses six indicators to identify ambulatory care patients who may benefit from pharmacists monitoring their medications: 1) five or more medications in present drug regimen; 2) 12 or more medication doses per day; 3) medication regimen changed four or more times during the past 12 months; 4) more than three concurrent disease states present; 5) history of noncompliance; and 6) presence of drugs that require therapeutic monitoring. Koecheler's tool is based on existing literature at the time of its development and expert panel opinions. The absence or presence of the final six indicators and their adverse outcomes were determined through a review of medication charts of 239 patients who visited internal medicine, general surgery, pediatric, and obstetric/gynecology clinics during five randomly selected weeks in 1985 and 1986. The results found that all six indicators were statistically significantly associated with increased risks for adverse outcomes, noncompliance being the strongest indicator.

4.2.3.2 Screening tools derived from Koecheler's risk predicting indicators

A year after Koecheler and colleagues published their risk predicting indicators Isaksen and colleagues (1999) published an article describing validation of a computer program developed to identify patients at risk for DRPs. The program was developed as a part of "The Impact of Managed Pharmaceutical care on Resource utilization and outcomes in Veterans Affairs Medical Centre" (IMPROVE) study (Carter et al. 1998). In this study the indicators of Koecheler and colleagues (1989) were automated using a computer program. Koecheler's indicators were also utilized as a basis of a screening tool of Barenholz Levy (Barenholz Levy 2003). This was the first geriatric-specific screening tool developed specially for use in ambulatory aged people and that could be self-administered by the patients to identify who is at a high risk for DRPs. The tool encompasses 10 risk predicting items (Table 6). Three years later in Canada, Langford and colleagues (2006) modified the questionnaire of Barenholz Levy to be used among all adult patients. The modified version of the questionnaire of Barenholz Levy (2003) was used in a randomized controlled study in order to determine whether a self-administered questionnaire improved identification of patients at risk for DRPs compared to standard care (Langford et al. 2006). The use of the risk assessment questionnaire led to a 3-fold higher patient referral to pharmacist-led drug therapy review than the standard care.

Koecheler's six indicators were also used by Australian researchers (Johnson et al. 2005) when they developed and tested a set of criteria to screen aged people at high risk for untoward medication events in community nursing caseloads focusing on adherence. Four predictors of complexity of medication and nonadherence were identified (Table 6, Figure 10).

Recently in Canada, studies of Koecheler (1998), Barenholz Levy (2003) and Langford (2006) were used to develop a self-administered screening questionnaire (Medication Risk Assessment Questionnaire, MRAQ) to be used in community pharmacies in order to identify patients having a large number of DRPs (Pammett et al. 2015, Figure 10). The tool has five risk predicting questions targeted for all adult patients.

4.2.3.3 Tools independent of Koecheler's indicators

In 2005, Fuller and Watson in the United Kingdom published an article about validation of a Self-medication Risk Assessment Instrument (Fuller and Watson 2005). The tool measures issues related to adherence, compliance and medication management (see Table 6). It was designed for older people living alone and was intended to be used by various health care workers (acute and community nurses, social service cares, pharmacists, GPs, and community therapists). It encompasses seven criteria that are based on evidence-based data relating to potential difficulties that individuals may have in managing their medications (Table 6). A score rating from 1 to 4 is allocated to each of the seven criteria to be assessed. Mental state, attitude and knowledge about medications and severe visual impairment demonstrated a high level of validity.

Another tool designed to screen aged people with unsafe medication management is a Swedish Safe Medication Assessment (SMA) tool (Gusdal et al. 2011, Table 6). The tool was developed on the basis of two successive working group recommendations for better use of medicines reports in Sweden (Gusdal et al. 2011). The tool is designed to be used by HC district nurses (DNs) and it highlights problems with adherence, concordance and medication management.

In order to describe the prevalence of risk factors for medication misadventures among older people in general practice in Australia a Medication Assessment Form was developed by Pit et al. in 2008 (Table 6). The form encompasses 31 items and was developed based on research evidence and expert opinions (Table 6). It was intended to be completed by patients themselves in the surgery while waiting for their physician's appointment. The main components of the form are: 1) awareness of the number of medicines used; 2) compliance issues; 3) problematic medicine classes; 4) adverse drug reactions; and 5) a recommendation section. The most common risk factors identified in the study of Pit and colleagues (2008) were: using any medicine longer than 6 months; having more than one doctor involved in care; having three or more health problems; or using more than five medicines. A subsequent study of Pit et al. (2007) indicated that the Medication Risk Assessment Form completed by the patients can be used to select patients for medication review.

A Swedish study produced and validated an instrument (PHASE-20) for the assessment of possible therapeutic drug-related symptoms among the aged (Hedström et al. 2009, Table 6). The instrument is based on seven pre-existing instruments (Hedström et al. 2009), which were coordinated and analyzed for content validity. PHASE-20 was tested in a randomized controlled trial among aged people living in nursing homes before and after the review of their medicines (Hedström et al. 2009). It encompasses 20 potential symptoms that may be related to medication (Table 6). The original version was intended to be used in nursing homes where a nurse or a carer assists the resident in completing the tool (Landstinget I Uppsala Län, 2014a). Later, a version to be used in outpatient care with instructions for the patient on how to complete the instrument was developed (Landstinget I Uppsala Län, 2014b). Also a PHASE-proxy version exists (Landstinget I Uppsala Län, 2014c). In 2010, The Swedish National Board of Health and Welfare recommended the use of the instrument (Landstinget I Uppsala Län, 2014d). Currently, it is used in most county councils in Sweden in connection with medication reviews.

In the UK, Barnett and colleagues (2011) developed a PREVENT tool (**P**hysical impairment, **R**isk from spesific med/medicines related admission, adh**E**rence issues, cogniti**V**e impairment, n**E**w diagnosis/exacerbation of disease, compli**N**ce, socie**T**al/social). The tool is intended to be used by pharmacists when visiting patients on admission to wards. The PREVENT tool supports identification of those patients who have unmanaged complex pharmaceutical issues and thus, are at increased risk of preventable medication-related readmissions and where the risk can be managed through pharmaceutical care (Barnett et al. 2011). Existing published tools, evidence from literature, action research and expert opinions were used as a basis for the tool.

4.2.3.4 Summary of geriatric specific screening tools

Altogether six geriatric specific screening tools for use in outpatient care were found (Barenholz levy 2003, Fuller and Watson 2005, Johnson et al. 2005, Pit et al. 2007, Hedström et al. 2009, Gusdal et al. 2011). Only the Australian screening tool (Pit et al. 2007) assessed risks of DRPs during the entire medication use process (Table 6). The tool of Barenholz Levy (2003) also is quite comprehensive but ignores e.g., symptoms suggestive of adverse drug reactions and the patient's social circumstances. Three of the tools (Fuller and Watson 2005, Johnson et al. 2005, Gushdal et al. 2011) concentrated on issues related to adherence, compliance and medication management. The Swedish Hedström's tool (2009) assessed only symptoms suggestive of adverse drug reactions, and thus, had no preventive point of view to DRPs. Number of the used medicines, changes in the medicines regimen during the past 12 months, more than one physician involved in patients care and issues related to non-adherence were the most often identified risks for DRPs. Two of the tools were designed to be completed by the patients themselves (Barenholz Levy 2003, Pit et al. 2007), Hedstöm's tool has versions for the patients, nurses and proxies (Hedström et al. 2009), others are designed to be completed by nurses (Johnson et al. 2005, Gusdal et al. 2011) or various health care professionals (Fuller and Watson 2005).

4.2.4 Criteria measuring inappropriate prescribing among the aged

Inappropriate prescribing can be defined as a situation in which the pharmacotherapy does not meet accepted medical standards (Hanlon et al. 2001). Knowing the fact that inappropriate prescribing is common among the aged, different criteria that measure inappropriate prescribing have been developed (Spinewine et al. 2007). The criteria can be classified as explicit or implicit (Table 7). Some criteria encompass both explicit and implicit criteria.

The US has been the forerunner in developing the criteria. The first explicit criteria were developed in 1991 by Mark Beers, MD, a geriatrician from the University of California, Los Angeles, as a guideline for nursing homes (Beers et al. 1991). The first implicit criteria Medication Appropriateness Index (MAI) was developed also in the US in 1992 by Hanlon and colleagues (Hanlon et al. 1992). Due to different selection of marketed drugs in different countries the applicability of Beers criteria is limited outside US (Dimitrow et al. 2011). Thus in 2008, Gallagher and colleagues developed a European tool called STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to the Right Treatment) (Gallagher et al. 2008). This explicit tool encompasses criteria measuring both potentially inappropriate prescribing and potential prescribing omissions.

These criteria can be used e.g., as prescribing guidelines, when assessing appropriateness of pharmacotherapy of the aged, in educational purposes and in research.

Table 7. *Characteristics of explicit and implicit criteria*

Explicit	Implicit
Criterion based	Clinical judgement based
Based on existing literature, or existing literature and clinical expertise of the investigators and/or existing criteria	Mostly developed in randomized controlled trials
Consensus validated	Validated using medical records of the participants
Generally used as rigid standards	Consider patient's entire drug regimen
Drug and/or disease oriented measuring pharmacological appropriateness of medication	Can account for patient's references
Can be applied with little or no clinical patient information	Rely on user's expertise Uses all available clinical patient information Time consuming
Need to be updated regularly	
Country specific	Not country specific

4.2.5 Deprescribing – A novel risk management approach

4.2.5.1 Evidence-based deprescribing guidelines

Although, it is well-known that polypharmacy and inappropriate medication use can cause DRPs, clinicians still find it difficult to change, reduce or stop medications (Cullinan et al. 2014). However, there may be medicines that have positive outcomes at a younger age but might be less beneficial or even harmful in the aging patient with several chronic diseases or geriatric syndromes (Tinetti et al. 2004). Several tools exist for assessing inappropriate medications and for starting needed medications (Spinewine et al. 2007), but no systematically developed guidelines have been published to help clinicians safely taper, reduce or stop medications which is called deprescribing (Farrell et al. 2015). In 2015, Canadian researches published the first priorities for deprescribing for elderly patients (Farrell et al. 2015). The article aimed to identify and prioritize medication classes where evidence-based deprescribing guidelines would benefit the clinicians. Twenty-nine drugs/drug-classes were included in three-round modified Delphi survey, 14 of which reached the required level (≥70%) of consensus. The Delphi panel encompassed 65 (the first round), 53 (the second round) and 47 (the third round) Canadian geriatric experts representing pharmacists, physicians and nurse-practitioners. The final five priorities the panelist rated to have an urgent and clear need for a deprescribing guidelines were: benzodiazepines, atypical antipsychotics, statins, tricyclic antidepressants, and proton pump inhibitors. The protocol for development and implementation of the first three evidence-

based guidelines for deprescribing in primary care and long-term care setting was published by Conklin and colleagues in June 2015 (Conklin et al. 2015).

4.2.6 Comprehensive Geriatric Assessment (CGA)

The above described risk management tools are extremely important, however, each of them targets only a small part of the whole problem (Budnitz et al. 2011). Comprehensive geriatric assessment (CGA) has been seen as "gold standard" of geriatric care as it serves as a most comprehensive tool to manage aged peoples' problems (including medicine use) comprehensively (Hickman et al. 2015). CGA is defined as "a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological and functional capabilities of a frail elderly person in order to develop a coordinated and integrated plan for treatment and long-term follow up" (Ellis et al. 2011). This global assessment of aged people and their problems allows more specific and sensible care paths for each single patient (Schmader et al. 2004). Patient centered medication reviews taking into account co-existing diseases or geriatric syndromes (e.g., falls, malnutrition, cognitive decline) as part of a global assessment of the aged people, are essential in CGA (Onder et al. 2013). Several models for CGAs exist (Hickman et al. 2015). The models may differ in settings they are developed for (nursing homes, acute geriatric units, hospitals), in composition of the interdisciplinary team (geriatricians, GPs, pharmacists, nurses, physiotherapists, social workers) and in clinical assessments conducted. According to a literature review of Onder and colleagues in 2011, compared to former risk management approaches, CGA may result in an improvement in the quality of prescribing and in a reduction in the risk of drug-related illness (Onder et al. 2011).

5 Strategies to prevent and resolve DRPs in geriatric pharmacotherapy in Finland

Since the early 2000s Finland has been actively involved in the European patient and medication safety initiatives (Council of Europe 2006a, Council of Europe 2006b). Medication safety is an essential part of patient safety since adverse drug events are found to be the most common single type of adverse events (Council of Europe 2006a, Ruuhilehto et al. 2011). According to a recent literature review regarding patient safety incidents in primary care, incidents relating to diagnosis and prescribing were the most likely to result in severe harm (Panesar et al. 2015). Older people with multiple diseases and complex medications are most vulnerable to harm caused by medications (Linden-Lahti et al. 2009, Panesar et al. 2015, Eronen 2016). This chapter focuses on initiatives taken in Finland to manage risks in geriatric pharmacotherapy.

5.1 Key initiatives to improve medication safety in geriatric pharmacotherapy in Finland

Figure 11 illustrates major initiatives to promote rational pharmacotherapy of the aged in Finland since 2006, when the Ministry of Social Affairs and Health published an expert report of the status of geriatric pharmacotherapy in Finland (Kivelä 2006).

A milestone in the efforts to improve medication safety of the aged was the Ministry of Social Affairs and Health's report on the quality of geriatric care in Finland (Kivelä 2006, Figure 11). The report particularly highlighted deficiencies in appropriateness and safety of geriatric pharmacotherapy in outpatient and inpatient care. According to the report, more basic and continuing education programs in geriatric pharmacotherapy for physicians, nurses and practical nurses should be made available. A national interprofessional program to prevent harmful effects of pharmacotherapies in older adults should be started, and in that context good medical and non-medical treatments should be developed especially regarding sleep disorders, depression, pain and dementia, and to prevent injuries from falling. "Current care" recommendations should be improved by including specific recommendations regarding the care of elderly people. Semiannual collaborative medication reviews involving all health care providers participating in the pharmacotherapy of the older individuals were recommended. The report also highlighted that practical nurses should be able to monitor the positive and negative effects of the medicines and their appropriate administration. The role of pharmacies in medication counselling was emphasized.

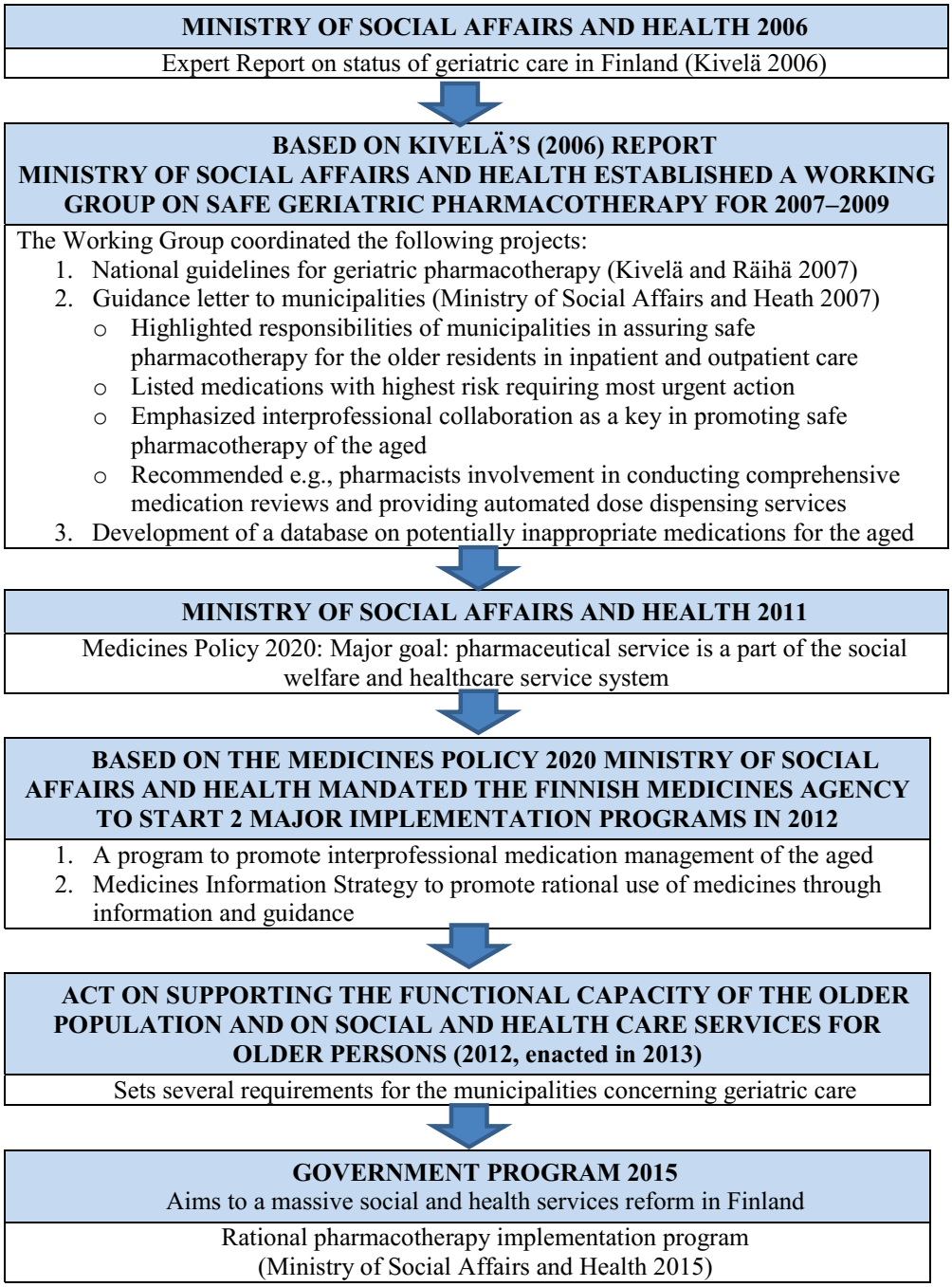

Figure 11 *Major policy initiatives to promote rational pharmacotherapy of the aged in Finland since 2006*

Based on the above-mentioned report by Professor Kivelä the Ministry of Social Affairs and Health established a Working Group on Safe Geriatric Pharmacotherapy for the period of 2007–2009 (Figure 11). The working group coordinated the implementation of several of the actions recommended by the report (see more details in the next paragraphs). The most remarkable long-term effect of the report was establishment of the Act on Supporting the Functional Capacity and Social and Healthcare Services for the Aged which was launched in 2013 (Act 980/2012). The Act aims to ensure accessibility of social and healthcare services for the aged, and thus, supports their independent living. The Act sets several requirements for the municipalities i.e., special expertise must be available at least in the field of promotion of wellbeing and health, gerontological care and social work, geriatrics, pharmacotherapy, nutrition, interprofessional rehabilitation and oral health care.

5.1.1 National guidelines on geriatric pharmacotherapy and a database of medication for the aged

The first national guidelines in geriatric pharmacotherapy "Pharmacotherapy of the Aged – Iäkkäiden lääkehoito" was published in 2007 by the National Agency for Medicines and the Social Insurance Institution (Kivelä and Räihä 2007, Figure 11). The guidelines are based on national and international studies and critical reviews. General principles and special features of geriatric pharmacotherapy but also detailed guidance on pharmacotherapy for diseases and symptoms common in aged population are described in the booklet. It also provides examples of medication reviews.

In 2008, the National Center for Pharmacotherapy Development (ROHTO) started the development of a database of medication for the aged (Lääke 75+) (Finnish Medicines Agency 2015a, Figure 11). The database encompasses information on potentially inappropriate and appropriate medications for the aged ≥75 years in order to support clinical decision-making for this special group of medicine users. Existing criteria measuring inappropriate prescribing and clinical consensus of expert opinions were used as a basis of the criteria (Ahonen 2011). The database is updated regularly by an expert group appointed by The Finnish Medicines Agency. The latest update was published at the end of 2015. Medicinal substances listed in the database are classified in four categories with color codes indicating how suitable each of the substances are for people aged ≥75 years. The categories are the following: A (green), suitable for the aged; B (grey), there is a little research evidence, practical experience or efficacy in persons over 75 years of age; C (yellow), suitable for the aged with certain precautions; and D (red), avoid using the substance for aged people. Each substance has a legend containing information on the effects, dosing and the most typical adverse reactions and interactions.

5.1.2 Medicines Policy 2020 and its implementation programs by Finnish Medicines Agency

The Ministry of Social Affairs and Health established "The Medicines Policy 2020" document in 2011 (Ministry of Social Affairs and Health 2011a, Figure 11). The document was developed in collaboration with the key stakeholders of the pharmaceutical sector (more than 40 stakeholder organisations, such as authorities, universities, professional organisations, pharmaceutical companies and patients).

According to the document, the main overall goal of pharmaceutical services by 2020 is to provide efficient, safe, rational and cost-effective pharmacotherapies to those who need them. The document emphasizes that pharmaceutical services are a part of the social welfare and health care service system and that client centeredness is a central goal in health care and pharmaceutical services. The document also highlighted the importance of patient empowerment and involvement in their own care. Interprofessional operational models and consultations in the implementation of the patient's pharmacotherapy should be strengthened both in outpatient and inpatient care. Medication management in a collaborative process throughout healthcare was prioritized among the key strategic areas. The tasks of various health care professionals in collaborative medication review processes should be defined. The document also emphasized the importance of accessibility to reliable and evidence-based medicines information sources for both healthcare professionals and medicine users.

Based on Medicines Policy 2020 Finnish Medicines Agency was mandated to start two major implementation programs in 2012 which focus on improving 1) interprofessional collaboration in medication management of the aged (Finnish Medicines Agency 2016, Figure 11) and 2) access and quality of medicines information to consumers and health care providers (Finnish Medicines Agency 2012, Figure 11).

The development network for improving interprofessional collaboration in medication management of the aged comprises of several local development teams from various social and health care settings throughout the country with physicians, nurses, pharmacists and other health care professionals as team members (Finnish Medicines Agency 2016). The core is to learn from these teams on how to make teamwork and what are the facilitators and barriers for interprofessional teamwork (Kallio 2014, Finnish Medicines Agency 2016). The ultimate goal of the network is to establish national guidelines for interprofessional medication management of the aged. The draft guideline was released for open hearing in the beginning of 2016 (Finnish Medicines Agency 2016). The draft guidelines emphasized development needs at structural, organizational and local network levels. It highlighted that current health care practices, including deficiencies in automated data transfer between, and even within, health care units, do not support patients' seamless care that assures safe and rational pharmacotherapy.

The main goal of the National Medicines Information Strategy, established in 2012, is to promote the rational use of medicines through information and guidance (Finnish Medicines Agency 2012, Hämeen-Anttila et al. 2012 and 2013). The key idea is to promote and coordinate the use of existing medicines information sources among the public and within social and health care services. The strategy also emphasizes taking into account

medicines information needs of special populations, the aged being mentioned among them. For them the strategy encourages to the development of new easy-to-read information sources. Challenges in the readability of package leaflets (e.g., small font size or too detailed text) was also noticed. The implementation of the medicines information strategy is also based on a network model.

5.1.3 Government Program 2015 and an implementation program on rational pharmacotherapy by the Ministry of Social Affairs and Health

Most recently, the importance of rational pharmacotherapy was acknowledged in the Finnish government program established in May 2015 (Government Program 2015). The government program aims to carry out a massive social and health services reform with the goal of improving implementation of comprehensive patient care, people's functional capacity, and creating conditions for rational and cost-effective pharmacotherapy from the perspectives of the patient and society. The importance of clinical medication reviews among the aged is also mentioned (Ministry of Social Affairs and Health 2016b). The Ministry of Social Affairs and Health established the implementation program for rational pharmacotherapy in November 2015 (Ministry of Social Affairs and Health 2015). The implementation program will operate through a steering group and four working groups. The working groups will focus on 1) rational prescribing, dispensing and use of the medicines; 2) social and health care structures and data systems supporting rational pharmacotherapy, 3) evidence to guide the establishment of rational pharmacotherapy and 4) drug innovations to support rational pharmacotherapy.

5.2 Inventory of essential tools and services available in Finland for assuring safe pharmacotherapy of the aged

In Finland, several tools exist to ensure medication safety in general, or specifically among the aged medicine users (Table 8). These tools have been developed for use by health care professionals or by the medicine users. Although only part of the tools are geriatric specific (G), they all can be utilized in order to improve medication safety of the aged. The tools range from product-specific medicine information databases to integrated systems assisting in clinical medication reviews (Table 8). The most extensive and widely used is the National Health Portal (Terveysportti) maintained by the Finnish Medical Society Duodecim (Finnish Medical Society Duodecim 2016a). Terveysportti is available for a charge throughout the health care, including community pharmacies. A comprehensive set of general current care guidelines exist in Finland, but special current care guidelines on geriatric pharmacotherapy are missing (Dimitrow et al. 2013). However, most of the general current care guidelines include a special section on geriatric patient care. Table 8 lists the tools available in Finland for improving medication safety according to the primary target users (health care professionals and medicine users).

Table 8. *Tools and services available in Finland for improving medication safety in general or particularly among geriatric patients (modified from Holmström 2012, Airaksinen et al. 2012).*

Tool	G/A	Purpose	Producer, reference/link
Tools for use by health care professionals			
National Health Portal (Terveysportti) available throughout the health care, including community pharmacies (service subject to a charge)	A	Current care guidelines (available also in open access) Drug database Drugs and prices database Database for comprehensive medication assessment Database of drug interactions (**S**wedish, **F**innish, **IN**teraction **X**-referencing (SFINX)) and burden of adverse drug effects (**PHAR**macological **A**ssessment **O**n-line (PHARAO)) Medicine use in patients with renal failure or dysfunction (Renbase) Medicine use in patients with liver failure or dysfunction (Heparbase) A database of pharmacogenetics (GeneRx) Database of xreactions of drugs (Xreactbase) Evidence-based information on herbal products and food supplements (Herbalbase) Medicines and laboratory database Medicines consultation website (a guidance and a list of existing medicines information services)	Finnish Medical Society Duodecim 2016a www.terveysportti.fi
EBMeDS (The Evidence-Based Medicine Electronic Decision Support)	A	An electronic decision support system that brings evidence into practice by means of context-sensitive guidance at the point of care	Finnish Medical Society Duodecim 2016b http://www.ebmeds.org/web/quest/home?lang=eng
Database of medication for the aged (Lääke 75+)	G	Information of potentially inappropriate and appropriate medication for the aged >75 years	Finnish Medicines Agency 2015a http://www.fimea.fi/web/en/databases_and_registeries/medicines_information/database_of_medication_for_the_elderly

Pharmacotherapy of the Aged (Iäkkäiden lääkehoito)	G	National guidelines for geriatric pharmacotherapy	Kivelä and Räihä 2007 (Kapseli 35) https://www.fimea.fi/documents/160140/753095/17702_julkaisut_Kapseli35.pdf
Automated dose dispensing (ADD) in hospitals and primary care (P)	A	A service in which regularly used medicines are machine packed into unit-dose bags for each time of administration. In primary care, the pouches are delivered to patient's home. ADD should include medication reconciliation and review before the patient is entered into the service	Ministry of Social Affairs and Health 2016a
Comprehensive medication review (CMR) (P)	G	A collaborative procedure for identifying, solving and preventing drug-related problems. The procedure includes a structured scheme for patient interview and documentation	Ministry of Social Affairs and Health 2011a, Leikola 2012, Leikola et al. 2012
Different variations of medication and prescription reviews and medication reconciliation reviews in different social and health care settings	A	Review of an individual patient's medication by a physician, nurse, or pharmacist. Can be performed as an element of a normal physician's appointment, dispensing of the medicine at the pharmacy or distribution at a hospital ward or in home care	Ministry of Social Affairs and Health 2011a Finnish Medicines Agency 2016 (Draft) Medication check service (the Association of Finnish Pharmacies, 2014. http://www.apteekkariliitto.fi/media/3-apteekkariliitto.fi/liitto/vuosikatsaukset/vuosikatsaus_2014_en.pdf
The SALKO® database (P)	G	An electronic tool for assessing medication-related risks of an individual patient (e.g., anticholinergic and sedative load and potentially inappropriate medications in the aged). The SALKO database can be integrated in the electronic prescription processing systems used in community pharmacies (Salix, Maxx)	Association of Finnish Pharmacies SALKO is available for members of the Association of Finnish Pharmacies. Leikola et al. 2013a Leikola et al. 2013b: Poster presentation 2013 http://www.fip.org/abstracts
Procuro® database (P)	A	A separate module for community pharmacy dispensing system supporting medication management covering e.g., drug-drug interaction screening (SFINX), SALKO-database, drug formulary, Tietotippa (a brief review of the product labelling to help in counselling)	Pharmadata http://www.pharmadata.fi/services/helpota-laakeneuvontaa-ja-kokonaislaakityksen-seurantaa-procurolla/
Summary of Product Characteristics, (SPC)	A	Contains the information relevant to the use of the medicinal products and of importance to health care professionals	Finnish Medicines Agency 2015b http://spc.fimea.fi/indox/english/humspc.jsp

A guide for processing health care unit's pharmacotherapy plan and pharmaco-therapy plans for individual patients	A	National guidelines for health care units (e.g., elderly care home and assisted living) to establish a plan for safe medication practices (2005) Requirement of individual pharmacotherapy plan as a part of patient's treatment plan (2011)	Ministry of Social Affairs and Health 2005 and 2011 Health Care Act nro1326/2010 (enacted 2011) National Institute for Health and Welfare 2015 Document 2005: http://urn.fi/URN:NBN:fi-fe201504226645 Document 2011: http://urn.fi/URN:NBN:fi-fe201205085259 Document 2015: http://urn.fi/URN:ISBN:978-952-302-479-3
National guidelines for interprofessional medication management of the aged	G	A national recommendation for enhancing interprofessional collaboration in optimizing pharmacotherapy of the aged	Finnish Medicines Agency (open hearing on the first draft in January 2016) https://www.fimea.fi/documents/160140/765540/Ik%C3%A4ihmisten+l%C3%A4%C3%A4kkeiden+j%C3%A4rkev%C3%A4n+k%C3%A4yt%C3%B6n+edist%C3%A4minen+moniammatillisesti+Kansallinen+selvitys+ja+suositukset.pdf/bf57f5f4-9df3-4d98-85aa-accc6e2215a0
Guidelines to harmonize automated patient specific dose dispensing (Lääkkeiden potilaskohtaisen annosjakelun hyvät toimintatavat)	A	Guidelines aiming to harmonize the practices in patient specific automated dose dispensing (ADD) in outpatient and inpatient care	Ministry of Social Affairs and Health 2016a http://www.julkari.fi/handle/10024/129748
Tools for medicine users			
Medication card	A	Lääkekortti.fi (Medication card) is an electronic service for managing medication regimens of individual patients. It allows medicine users to store, modify and print information on their medications and vaccinations.	Pharmaceutical Information Centre https://laakekortti.fi/Frontpage.aspx Also other service providers e.g., Association of Finnish Pharmacies
KanTa-service (My Kanta pages)	A	Portal to medicine users own medical records and electronic prescriptions	Kansallinen Terveysarkisto (Kanta) 2016 http://www.kanta.fi/en/omakanta
The Health Library (Terveyskirjasto.fi)	A	National evidence-based, open access health and medicines information online database for consumers. Contains also a link collection of reliable medicine information sources.	Finnish Medical Society Duodecim 2016c http://www.terveyskirjasto.fi/terveyskirjasto/tk.koti
Fimea Safeguards the Pharmaceutical Services for the Public (Kansalaisen lääketieto)	A G	General information on safe and proper use of medicines and how to avoid counterfeit medicines. Contains a DARTS checklist for evaluating the reliability of medicine information. Encompasses a section: medication of the elderly.	Finnish Medicines Agency 2015d http://www.fimea.fi/web/en/for_public

Current care guidelines, patient versions	A	Each current care guideline in Finland (Käypä hoito) has a summary written in lay language targeted to patients.	Finnish Medical Society Duodecim 2016d http://www.kaypahoito.fi/web/kh/potilaalle
Database of medication for the aged (Lääke 75+)	G	An open access electronic database containing information on potentially inappropriate and appropriate medications for the aged (the same database is available for consumers and health care professionals)	Finnish Medicines Agency 2015a http://www.fimea.fi/web/en/databases_and_registeries/medicines_information /database_of_medication_for_the_elderly
Medicines Reminder service (P)	A	A service available in Finnish community pharmacies to remind the patient to take his/her medicines. The service encompasses a medication card for the patient.	Association of Finnish Pharmacies (also other applications and services available) http://www.apteekki.fi/apteekki-palvelut/laakkeenoton-muistutuspalvelu.html
Patient guide (Potilaan opas)	A	Part of national patient safety program aiming to encourage the patients to take more responsibility for their own care	National Institute for Health and Welfare 2016 http://www.potilaanopas.fi/en/index.html
Package Leaflets PL	A	Provides medicine users with information about the medicinal product and its correct use.	Finnish Medicines Agency 2015c http://spc.fimea.fi/indox/english/humpil.jsp
University Pharmacy call center Yliopiston Apteekin tietopalvelu	A	National interactive medicines information service for all medicine users available 24 hours a day	University Pharmacy http://verkkojulkaisu.viivamedia.fi/yliopistonapteekki/vuosikertomus2014/6
Abbreviations: A=Tool for all medicine users, G=geriatric-specific tool, P=Tool developed to be used or delivered in community pharmacies, DARTS=**D**ate, **A**uthor, **R**eference, **T**ype, **S**ponsor (Närhi et al. 2008)			

5.3 Medication risk management initiatives in Finnish community pharmacies

5.3.1 Pharmacy-led initiatives towards more clinically oriented services

As an increasing proportion of aged people live in their own homes, the role of community pharmacies in promoting medication safety among the aged medicine users is growing. Finnish community pharmacies have actively taken action to promote the safe use of medicines (Tippa Project 2014, Airaksinen et al. 2012, Leikola 2012). The first long-term coordinated effort was the TIPPA program (in English: Customized Information for the Benefit of the Patient from the Community Pharmacy) in 2000–2003, which aimed to improve patient safety by improving patient counselling (Tippa Project 2014, Puumalainen 2005, Kansanaho 2006). The program was coordinated by the authorities, universities, continuing education centers and professional organizations. Improved patient counselling led to increasing communication between pharmacists and patients (Kansanaho et al. 2005). This, in turn revealed several problems the people have with their medications and that could not be resolved by counselling, but required more comprehensive review of the medications. Thus, a follow-up program for TIPPA in 2004–2007 was implemented focusing on multidisciplinary collaboration and meeting the needs of medicine users (Tippa Project 2014). The key was to start accreditation training program for pharmacists to acquire clinical skills needed in comprehensive medication reviews (Tippa Project 2014, Peura et al. 2007, Leikola et al. 2009). This initiated a new chapter in the development of Finnish community pharmacy practice and extending services from dispensing to clinically-oriented collaborative services.

5.3.2 Comprehensive medication review and other medication review/check services in community pharmacies promoting medication safety of the aged

The Association of Finnish Pharmacies (AFP) has coordinated several pharmacy services related to medication risk management. In addition to the AFP, University Pharmacy also has developed its own modifications of the services.

The CMR is the most important pharmacy service developed under the TIPPA follow-up program (Leikola 2012, Tippa Project 2014). CMR is a collaborative procedure for identifying, solving and preventing DRPs and is especially targeted to geriatric patients (Table 8, Leikola 2012, Leikola et al. 2012). In CMR, an accredited pharmacist (1 ½ year curriculum (35 ECTS credits) encompassing distance and face-to-face learning) collaborates closely with health care professionals, especially with the patient's physician. Patient's clinical information (i.e., diagnoses, medications, laboratory results) is provided to the pharmacist by the physician. The pharmacist interviews the patient (and, if needed, the caregivers and/or nurses are involved) at the patient's home using a structured scheme for patient interview and documentation. After a comprehensive review of the medications the pharmacist writes a report with findings and recommendations for the physician. To determine the actions, the report is discussed with the physician (possibly accompanied by the nurse) face-to-face. A follow-up interview with the patient is conducted after approximately 3 months.

During the last years, CMR has stimulated discussion about geriatric pharmacotherapy risks and their management, and how pharmacists could take part in medication reviews (Ministry of Social

Affairs and Health 2011b, Ministry on Social Affairs and Health 2013). As CMR is a hard and time consuming process and realizing the fact that lighter, more easily out carried processes work in several medicine users, lighter versions have been modified (Ministry of Social Affairs and Health 2011a, Table 8). Being the first really collaborative process in Finland, CMR has also met resistance in Finnish health care. However, according to a study conducted in 2013 as a national online survey, Finnish pharmacy owners are interested in developing medication review services, if the services would have national criteria and funding (Jokinen et al. 2014). The range of actual services available at the time of the study (year 2013; respondents: n=198) was the following: automated dose dispensing (ADD, discussed in next paragraph); 77%, medication review services; 23%, CMR; 21% (Jokinen et al. 2014).

5.3.3 Automated dose dispensing services by community pharmacies

Automated dose dispensing (ADD) is a collaborative service provided by community pharmacies in primary care. ADD means that patient's regularly used medicines are machine packed into unit-dose bags for each time of administration (Sinnemäki et al. 2013 and 2014, Ministry of Social Affairs and Health 2016a). The pouches are delivered to the patient's home, assisted living facilities or nursing homes. ADD service encompasses medication reconciliation followed with medication review conducted with interprofessional cooperation before the patient is entered into the service (Ministry of Social Affairs and Health 2016a). During the service, at least annual medication reviews are recommended. Although ADD services have been available for several years in Finland, ADD start-up processes may still vary between different service providers (Sinnemäki et al. 2014). The new guidelines published by the Ministry of Social Affairs and Health (2016) aim to harmonize the practices.

5.3.4 Tools to support medication safety in community pharmacies

Finnish community pharmacies have excellent tools available for managing medication risks (see Table 8). Among the most important ones from the geriatric pharmacotherapy perspective is SALKO database, a medication review tool specifically designed to be used in community pharmacies (Leikola et al. 2013a and b). The SALKO database was developed by the Association of Finnish Pharmacies (AFP) to assist community pharmacists in evaluating medication-related risks among aged patients. SALKO is maintained by AFP and is updated regularly. The SALKO indicates sedative, anticholinergic and serotonergic properties of the medications, appropriateness for the elderly based on 4 different criteria (Laroche et al. 2007, Socialstyrelsen 2010, AGS 2012, Finnish Medicines Agency 2015a) and metabolization via 6 different Cytochrome P450 (CYP) enzymes.

5.4 Recent policy initiatives regarding community pharmacists' involvement in managing safety risks in geriatric pharmacotherapy

The role of community pharmacies in promoting safe pharmacotherapy has been discussed in two reports by The Ministry of Social Affairs and Health since 2011 (Ministry of Social Affairs and Health 2011b, Ministry on Social Affairs and Health 2013). Regarding especially the aged medicine users with multiple medications, the first working group on the development of pharmacy services identified the following development needs: to further develop the automated dose dispensing procedure, to develop quality standards for medication reviews and to carry out a study to evaluate their cost-effectiveness (Ministry of Social Affairs and Health 2011b).

In 2013 the Finnish Medicines Agency was again mandated by the Ministry of Social Affairs and Health to identify development needs regarding pharmaceutical services in both outpatient and inpatient care (Ministry on Social Affairs and Health 2013). The final report emphasizes that pharmacies and hospital pharmacies should have a greater responsibility in promoting rational pharmacotherapy. These reports provide a foundation for structuring pharmaceutical services as part of social and health care services, which are currently under reform (Government Program 2015).

6 An overwiew of Finnish studies on medicine use known to be potentially harmful for the aged

6.1 Literature search

A literature search of PubMed was performed using surnames of Finnish senior researchers known to be experts in geriatric care and geriatric pharmacotherapy. The search terms were: *Ahonen J, Bell JS, Enlund H, Finne-Soveri H, Hartikainen S, Hosia-Randell H, Huupponen R, Isoaho R, Jyrkkä J, Kivelä SL, Leikola S, Linjakumpu T, Nurminen J, Pitkälä K, Puustinen J, Strandberg T, Sulkava R, Taipale H, Tilvis R, Räihä I, Salonoja M.* English language peer reviewed articles published between 1.1.2000–31.12.2015 describing studies conducted in Finland among people ≥65 years were searched with no limitation on the type of study. This overview has no aim to address the results of the studies but it focuses on what different aspects has been studied on medicine use that can be potentially harmful for the aged.

6.2 Results

Altogether 75 research articles were found. Majority (87%; n=65/75) of the articles focused on describing trends in medication use among the aged, polypharmacy and potentially inappropriate prescribing and medicine use (Figure 12). Minority (13%; n=10/75) described interventions aiming to reduce potentially inappropriate prescribing or medicine use and/or influence of these interventions. The distribution of these articles over time is presented in Figure 12.

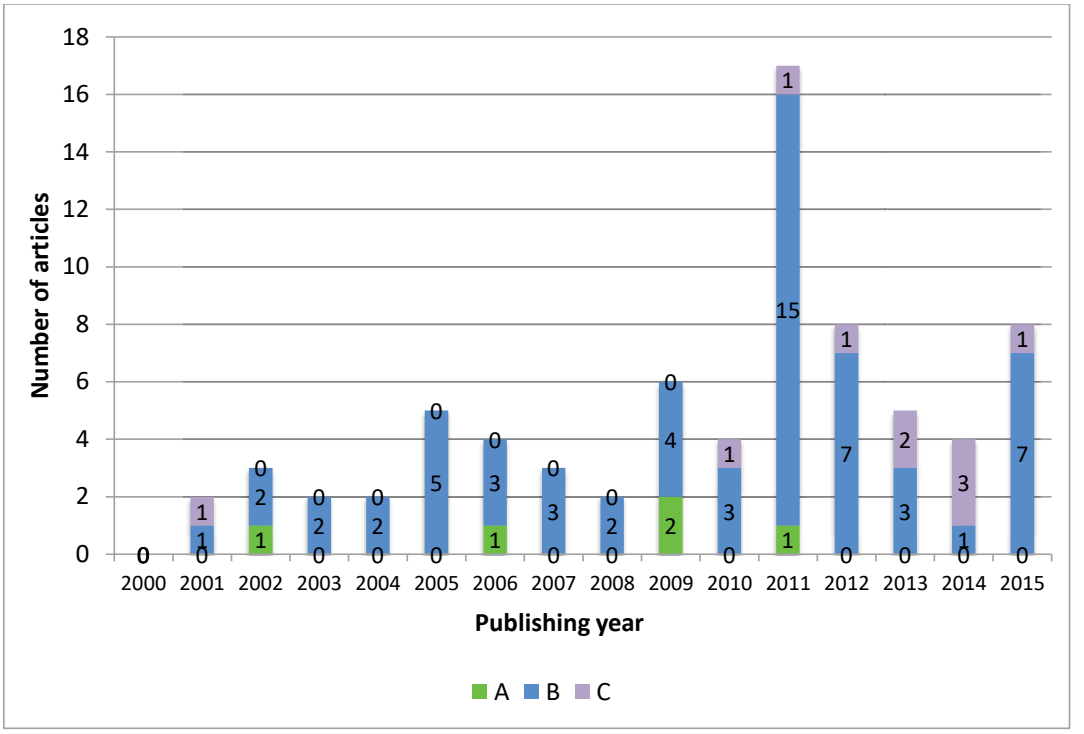

Figure 12 *Distribution over time of the research articles describing A) polypharmacy, B) potentially inappropriate prescribing and medicine use C) interventions aiming to reduce potentially inappropriate prescribing and medicine use in Finland since 2000 (number of articles according to the publication year)*

6.2.1 Articles describing medicine use known to be potentially harmful for the aged

6.2.1.1 Trends in medication use of the aged regarding polypharmacy

Altogether five (7%) studies described polypharmacy (Linjakumpu et al. 2002, Jyrkkä et al. 2006, Jyrkkä et al. 2009a and b, Jyrkkä et al. 2011, Table 9). Most of these articles were prevalence studies (prevalence, changes in prevalence over time) and were conducted in outpatient care in local communities.

Table 9. *Summary of Finnish studies reporting trends in medication use of the aged regarding polypharmacy (n=5)*

Study	Definition of polypharmacy	Population/health care setting	Data source, year	Study objectives
Linjakumpu et al. 2002	>5 medicines used	Home-dwelling persons aged ≥64 years in Lieto n=1 131 residents in 1990–1991 n=1 197 residents in 1998–1999	Interviews conducted by a trained nurse (The subjects had been informed to bring their prescription forms and drugs with them to present the medication that they were currently taking) Health examination by two health center physicians 1990–1991, 1998–1999	Changes in medicine use and polypharmacy
Jyrkkä et al. 2006	>5 medicines used Excessive polypharmacy: ≥10 medicines used	Persons aged ≥75 years in Kuopio n=601 in 1998 (4 % (n=13) in institutional care) n=339 in 2003 (15 % (n=50) in institutional care	Interview of a trained nurse (medicine use was assessed based on medicine containers and prescriptions). Physician/geriatrician reviewed medications after the nurse interview Kuopio 75+ Study[1)], 1998, 2003	Changes in medicine use, polypharmacy and excessive polypharmacy between 1998–2003 among a cohort
Jyrkkä et al. 2009a	>5 medicines used Excessive polypharmacy: ≥10 medicines used	Home-dwelling aged ≥75 years in Kuopio (n=523)	Interview of a trained nurse (medicine use was assessed based on medicine containers and prescriptions). Physician/geriatrician reviewed medications after the nurse interview and examined the participants and diagnosed their current diseases Kuopio 75+ Study[1)], 1998	To describe the number and types of medicines used and to evaluate the role of different factors associated with polypharmacy and excessive polypharmacy

Jyrkkä et al. 2009b	>5 medicines used Excessive polypharmacy: ≥10 medicines used	Community-dwelling aged ≥75 years in Kuopio (n=601; home-dwelling n=523, institutionalized n=78) followed 1998–2002 Survivors aged ≥80 years (n=339; home-dwelling n=286, institutionalized n=50) followed 2003–2007	Interview of a trained nurse (medicine use was assessed based on medicine containers and prescriptions). A trained nurse and a geriatrician examined the participants' health status and checked their medical records (1998) The follow-up examinations conducted using the same set of procedures as the baseline examination, except that there was no clinical examination by a geriatrician (2003) Kuopio 75+ Study[1)], 1998–2007	To assess whether polypharmacy or excessive polypharmacy could be indicator of mortality
Jyrkkä et al. 2011	>5 medicines used Excessive polypharmacy: ≥10 medicines used	Community-dwelling aged ≥75 years in Kuopio (n=294)	Drug containers and prescriptions Clinical examinations; nutritional assessment, cognition, functional ability GeMS Study[2)], 2004–2007	Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period

[1)]Kuopio 75+ Study: Cohort study that focuses on the clinical epidemiology of diseases, drug use and functional capacity in elderly persons. Community-dwelling age ≥75 years and living in the city of Kuopio, Finland were included in the study (n=4 518). A random sample of 700 persons was drawn from this population on January 1, 1998. A follow-up of survivors was conducted in 2003.

[2)]GeMS (Geriatric Multidisciplinary Strategy for the Good Care of the Elderly) Study: 1000 randomly selected persons aged ≥75 years (born before 1 November 1928) living in the city of Kuopio, Finland, in November 2003 were invited to participate in the study. These persons were randomized to intervention (i.e., receiving CGA; n=500) and control (i.e., receiving standard care; n=500) groups. The baseline examination was conducted in 2004, with follow-ups performed in 2005, 2006 and 2007. At the beginning of 2004, the City of Kuopio had a population of 88 253 inhabitants, 5615 of whom were aged ≥75 years. The CGA (Comprehensive Geriatric Assessment) included clinical examinations, medication assessment and interventions to improve nutritional state and functional capacity conducted in multidisiplinary team of 2 physicians (trainees in geriatrics), 2 physiotherapists, and 1nutritionist.

6.2.1.2 Potentially inappropriate prescribing and medicine use

A majority (81%, n=60) of the articles described potentially inappropriate prescribing and medicine use (Table 12). Of them, 40 (66.6%) were conducted in outpatient care (Table 10). Registers, patient interviews and patient interview and medical records/charts were most often used as a source of data. These studies most often reported prevalence of the use of potentially harmful medicines, changes in the use of these medicines, factors associated with the use and/or the association between the use of those medicines with predominantly determined ADEs (e.g., falls, fractures, cognitive decline, delirium, orthostatic hypotension, poor muscle strength or balance) or other outcomes (e.g., hospitalization, health service utilization, mortality, morbidity, psychological well-being). Table 10 shows the settings and study populations of the studies describing inappropriate prescribing and medicine use in the aged.

Table 10. *Settings and study populations of the studies describing inappropriate prescribing and medicine use in the aged (n=60)*

Setting	**% (n)**
Outpatient care	66.6 (40)
Long-term care	21.6 (13)
Outpatient care and long-term care	5 (3)
Hospital setting	1.7 (1)
Long-term care and hospital setting	1.7 (1)
Acute ward	1.7 (1)
During admission	1.7 (1)
The size of the study population	**% (n)**
1–100	0 (0)
101–200	5 (3)
201–500	15 (9)
501–1000	30 (18)
1001–10 000	35 (21)
10 001–100 000	13 (8)
>100 000	2 (1)

Of the 60 articles, six (10 %) described studies using existing criteria as measures of appropriateness, such as Beers criteria or categorization of the Finnish Medicines Agency for potentially inappropriate medicine use among the aged (Pitkälä et al. 2002, Fialova et al. 2005, Raivio et al. 2006, Hosia-Randell et al. 2008, Leikola et al. 2011, Bell et al. 2013, Tables 11 and 12). Of these studies, only one study covered the entire Finnish non-institutionalized population aged ≥65 years (n= 841 509) (Leikola et al. 2011). Single medicines, medicine groups or medicine combinations known to be harmful for the aged were studied in 90% (54/60) of the articles (Tables 11 and 12). Of these, Central Nervous System (CNS) medications was the most studied therapeutic group (81%, n=44), antipsychotics, anticholinergics and sedatives being the most studied subgroups.

Table 11. *Measures of potentially inappropriate prescribing and medicine use used in the studies (n=60)*

Measure	n
Existing criteria, total	**6**
Beers 1997 criteria (Beers 1997)	2
Beers 2003 criteria (Fick et al. 2003)	1
Beers 2003 criteria (Fick et al. 2003) + SFINX-interactions	1
Database of medication for the elderly (Finnish Medicines Agency 2011)	1
Beers 1997 (Beers 1997), 2003 (Fick et al. 2003) and McLeod criteria (McLeod et al. 1997)	1
Medicines, medicine groups and combinations of medicines, total	**54**
Central Nervous System (CNS) medicines (total)	44
CNS-medicines (the entire group)	1
Psychotrophics	9
Psychotrophics and analgesics	1
Psychotrophics and sedatives	1
Psychotriphics, analgesics and opioids	1
Antipsychotics	8
DAPs	6
DAPs and sedatives	3
DAPs, sedatives and antipsyhotics	1
DAPs and ChELs	1
Sedatives	10
Antidepressants	1
Antiepilectics	1
Other medicines and medicine groups, total	9
Analgesics	3
Opioids	1
SSRIs, NSAIDs/Aspirin and gastroprotective medicines	1
Laxatives (regularly)	1
PPIs	1
All used medicines	1
Prescription medicines	1
Interactions, total	1
Drugs interacting with warfarin	1

ChEL=Cholinesterase Inhibitor, DAP=Drug with anticholinergic properties, SFINX= **S**wedish, **F**innish, **I**nteraction **X**-referencing database, SSRI=Selective Serotonin Reuptake Inhibitor, NSAID=Nonsteroidal Anti-Inflammatory Drug, PPI=Proton Pump Inhibitor

Table 12. *Summary of Finnish studies investigating potentially inappropriate prescribing and medicine use (n=60)*

1. Studies using existing criteria measuring inappropriate prescribing and medicine use among the aged (n=6)				
Study	**Measure of inappropriate prescribing**	**Population/health care setting**	**Data source, year**	**Study objectives**
Pitkälä et al. 2002	Beers 1997 criteria	Random sample of 3921 (of which 3219 were home dwelling) elderly urban residents aged 75, 80, 85, 90 and 95 years. Helsinki	Questionnaires completed by the participants (mail survey) 1998–1999	Prevalence of a) potentially inappropriate medicines b) medicines considered inappropriate related to 15 common medical conditions
Fialova et al. 2005	Beers 1997, Beers 2003, McLeod 1997 criteria	Home care clients ≥65 years (n=187) from Helsinki	An interview at the client's home, results of Comprehensive Geriatric Assessment 2001, 2002	Prevalence and associated factors of potentially inappropriate medication use in 8 European countries (Czech Republic, Denmark, Finland, Iceland, Italy, Norway, The Netherlands, The United Kingdom)
Raivio et al. 2006	Beers 1997 criteria	A total of 425 patients (mean age 86 years) admitted to 7 nursing homes (n=195) and 2 geriatric hospitals (n=230). Patients with dementia were studied as a subgroup Helsinki	Medical records Mortality, days in acute hospital: central registers during 2-years of follow up (2002) 1999–2000	a) prevalence of users of diagnosis-independent potentially inappropriate medicines (PIMs) in regular daily use, b) their impact on mortality and use of health services
Hosia-Randell et al. 2008	Beers 2003 criteria, **S**wedish, **F**innish, **I**nteraction **X**-referencing (SFINX) database	Nursing home residents aged ≥65 (mean age 83.7) years (n=1 987) Helsinki	Medical charts 2003	a) extent and nature of regularly prescribed diagnosis-independent PIMs b) possibility of clinically significant drug-drug interactions that should be avoided
Leikola et al. 2011	Beers 2003 criteria	The entire non-institutionalized population in Finland aged ≥65 years (n=841 509)	Reimbursement data from Social Insurance Institution 2007	a) prevalence of diagnosis-independent PIM use b) reimbursement costs for PIMs
Bell et al. 2013	Categorization of The Finnish Medicines Agency (2010) for potentially inappropriate drug use among aged ≥75 years	781 participants from a random sample of 1 000 persons aged ≥75 years: 81 (10 %) institutionalized, 700 (90%) home-dwelling Kuopio	Patient interview by a trained nurse Medicine use verified against medical records GeMS Study[1)] 2004	Factors associated with the use of one or more Category D medicines (i.e., according to the categorization of The Finnish Medicines Agency classified as inappropriate for the aged)

2. Studies using drugs/drug groups/drug-drug interactions known to be harmful for the aged (n=54)				
Study	**Drugs/drug groups/drug-drug interactions**	**Population/ health care setting**	**Data source, year**	**Study objectives**
		2001		
Pajukoski et al. 2001	All regularly used prescribed medicines Medical diagnoses	Home-dwelling aged who were hospitalized because of sudden worsening of their general health (n=175, mean age with SD, 82±5.7 years) For comparison, home-dwelling aged outpatients (n=252, mean age with SD, 77±5.7 years) Acute geriatric ward at Harjula Hospital, Kuopio	Medicines and medical diagnoses: medical records obtained during admission verified by the health care staff Patient's subjective feeling of dry or burning mouth: a structured questionnaire Saliva samples Outpatients: Patient interviews, patients were asked to bring their prescriptions for review (OTC-medicines were excluded) Year: not mentioned	Prevalence of self-reported symptoms of dry mouth and burning mouth Relationship between the symptoms and systemic diseases and medication For comparison, home-dwelling aged of the same community were studied
		2002		
Linjakumpu et al. 2002	Psychotropics (antipsychotics, anxiolytics, hypnotics, antidepressants)	Home-dwelling aged ≥64 years in Lieto: n=1131 residents in 1990–1991 n=1197 residents in 1998–1999	Two cross-sectional patient interviews by a trained nurse and health examination surveys National prescription data from Social Insurance Institution for comparison of all Finnish elderly and elderly in Lieto in late 1990s 1990–1991 and 1998–1999	Prevalence and changes in the use of psychotropics in 1990s

2003				
Hartikainen et al. 2003a	Psychotropics, (antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives)	Home-dwelling aged ≥75 years in Kuopio (n=523) extracted from a random sample of 700 individuals	Patient interview about the use of medicines and clinical examinations conducted by a geriatrician and a trained nurse Kuopio 75+ Study[2)], 1998	To describe the use of psychotropics in demented and non-demented people aged ≥75 years living in a Finnish city with 80 000 inhabitants (Kuopio)
Hartikainen et al. 2003b	Psychotropics, (antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives)	Home-dwelling aged ≥75 years in Kuopio (n=523), extracted from a random sample of 700 individuals	Patient interview about the use of medicines and clinical examinations conducted by a geriatrician and a trained nurse Kuopio 75+ Study[2)], 1998	To describe the use of psychotropics in home-dwelling residents aged ≥75 years in a Finnish city with 80 000 inhabitants (Kuopio)
2004				
Linjakumpu et al. 2004	Sedatives	Home-dwelling aged ≥64 years in Lieto (n=1 197)	A cross-sectional patient interview and a health examination survey 1998–1999	Prevalence of the use of sedative drugs and drugs with sedative properties Association with the use of sedatives and demographic or health items (e.g., self-perceived health, dementia, mobility problems, depression)
Pitkälä et al. 2004	Psychotropic drugs (antidepressants, antipsychotics, anxiolytics, Cholinesterase Inhibitors (ChEls), Drugs with anticholinergic properties (DAPs), hypnotics)	Patients aged >70 years with dementia in six acute geriatric wards in two city hospitals and seven nursing homes in Helsinki (n=425)	Comprehensive patient interview, cognitive tests, and attention test 1999–2000	Prevalence of various psychiatric and behavioral symptoms among patients with dementia To investigate the administration of psychotropic medications to these patients
2005				
Hartikainen et al. 2005a	Psychotropics (antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives)	Home-dwelling aged ≥75 years (n=77) in Kuopio Institutionalized aged over ≥75 years (n=60) extracted from a random sample of 700 individuals in 1998	Patient interview, medical records Mortality data: Statistics Finland 1998–2003 Kuopio 75+ Study[2)], 1998–2003	The use of psychotropics and its relation to mortality in demented elderly people in years 1998–2003

Hartikainen et al. 2005b	Analgesics	Home-dwelling aged ≥75 years in Kuopio (n=523) extracted from a random sample of 700 individuals	A patient interview by a nurse for which the patients were asked to bring their prescriptions and drugs including over-the-counter (OTC) products that they were currently using Kuopio 75+ Study[2)], 1998	The use of analgesics and its relationship to daily pain and morbidity
Hartikainen et al. 2005c	Psychotropics (antipsychotics, antidepressants, anxiolytics, hypnotics/sedatives) and analgesics	Home-dwelling aged ≥75 years (n=523) extracted from a random sample of 700 individuals in Kuopio	Patient interviews and clinical examinations conducted by a geriatrician and a trained nurse Kuopio 75+ Study[2)], 1998	Extend of concomitant use of analgesic and psychotropic medicines
Hosia-Randell and Pitkälä 2005	Psychotropics (antipsychotics, anxiolytics, antidepressants, hypnotics)	Long-term nursing home residents ≥65 years with and without dementia in Helsinki (n=1 987)	Medical charts 2003	To describe the use of psychotropics in all residents with and without dementia
2006				
Alanen et al. 2006a	Antipsychotics	Institutionalized aged 90–107 years, mean age 92.9±2.7 years 3 identical cross-sectional samples; each data set included 3662–3867 resident assessments originated from 16 hospital-based institutions and 25 residential homes located in different parts of Finland	Resident Assessment Instrument (RAI) database consisting of Minimum Data Set (MDS) assessments version 2.0 for long-term care facilities RAI located in STAKES 2001, 2002, 2003 (1.7.–31.12. each year)	Use of antipsychotic medications, change over time and associated factors in a three year follow-up
Alanen et al. 2006b	Antipsychotics	Institutionalized aged ≥ 90 years (n=1334) Resident assessments originated from 23 hospital-based institutions and 43 residential homes in different parts of Finland	Resident Assessment Instrument (RAI) database consisting of Minimum Data Set (MDS) assessments version 2.0 for long-term care facilities RAI located in STAKES 1.1.–30.6.2003	To analyze the factors associated with the use of antipsychotic medication among nonagenarian (people aged 90–99 years) residents

2007				
Hosia-Randell et al. 2007	Regular use of laxatives	Institutionalized aged ≥65 years (mean age 83,7 years) from all nursing homes of Helsinki (n=1987)	Medical charts 2003	Prevalence of regularly administered laxatives To identify factors associated with regular use of laxatives and to determine which drug classes or medications are associated with regular laxative use
Puustinen et al. 2007	Benzodiazepines and related drugs	Patients aged ≥65 years admitted to acute hospital wards during 1 month in Pori (n=164)	Patient interview and checking the prescriptions on admission to hospital 2004	Associations between the use of benzodiazepines or related drugs and health, functional abilities and cognitive function
Raivio et al. 2007	Atypical and conventional antipsychotics	Institutionalized aged ≥70 years (mean age 86 years) with (n=254) and without dementia (n=170) from Helsinki	Medicine use: medical records Mortality: central registers 1999–2000	To examine the impact of atypical and conventional antipsychotics on mortality and hospital admissions in two years follow-up and to compare their prognosis with that of nonusers
2008				
Alanen et al. 2008	Antipsychotics	Home-dwelling aged ≥65 years (n=1106) from five home care units in different parts of Finland (urban and rural)	Resident Assessment Instrument (RAI) database consisting of Minimum Data Set for Home Care (MDS-HC) RAI located in STAKES 1.7.–31.12.2004	Use of antipsychotic medications, and factors associated with their use
2009				
Hiitola et al. 2009	All medicines used	Home-dwelling aged ≥75 years with orthostatic test (n=653) extracted from a random sample of 1000 patients in Kuopio	A patient interview conducted by a trained nurse The patients were asked to bring their prescriptions and medicine containers with them for the interview Data from medical records GeMs Study[1)] 2003	Investigation of postural changes in blood pressure and heart rate and assessing the prevalence of orthostatic hypotension (OH) and its association with the medicines used

Panula et al. 2009	Anticholinergics, sedatives and antipsychotics	Hip fracture surgery patients aged ≥65 years in Satakunta hospital district (n=461)	Finnish National Hospital Discharge Register Death statistics in Finland Population-based data collected during a 2-year period 1999–2000	To describe relationships between use of sedatives, antipsychotics or potential anticholinergics and postoperative mortality in patients with hip fractures
Taipale et al. 2009	Sedatives	Residents of long-term facilities (mean age 81,3 years; 23–104) in Helsinki (n=1 004)	Drug-use data: medication administration charts Mortality: central registers 2003	Sedative load and possible association between sedative load and mortality
Uusvaara et al. 2009	Anticholinergics	Home-dwelling people aged 75–90 years without clinical dementia (n=400) but with a history of stable atherosclerotic disease in Helsinki	A comprehensive clinical assessment by a study nurse and a geriatrician-internist Diagnoses: medical records Medicines: self-report in the mailed questionnaire and bringing the drug packages to the clinic, verification from medical records DEBATE Study[3)] baseline assessments in 2000	To clarify the association between anticholinergic drugs and apolipoprotein E ε4 allele carrier status (APOE4)[4)] and cognitive dysfunction
2010				
Nurminen et al. 2010	Psychotropics (BZDs, antipsychotics, antidepressants)	Home-dwelling aged ≥65 years in Lieto (n=1 177)	A cross-sectional patient interview and a health examination survey Information about fractures confirmed with radiology reports was individually collected from the medical records from the baseline until the end of 1996 1990–1991, 1996	Gender-specific associations between the use of psychotropic drug, or the concomitant use of two or more of these drugs and the risk of fractures

Pokela et al. 2010	Analgesics (prescription and non-prescription analgesics)	Home-dwelling people age ≥75 years (n=700) drawn from the initial sample of 1 000 aged from population register in Kuopio	Patient interviews by a nurse and needed tests to assess physical function, self-rated mobility, cognitive function, presence of depressive symptoms, self-rated health (self-reported drug utilization data was verified against medical records) GeMS Study[1)] 2004	Prevalence of analgesic use. To investigate factors associated with daily and as-needed analgesic use
Teramura-Grönblad et al. 2010	Proton Pump Inhibitors (PPIs)	Frail nursing home residents (mean age 83.7 years) in Helsinki (n=1 987)	Medical charts Trained nursing home personnel assessed the residents' health status 2003	Use of PPIs and their associated risks
2011				
Bell et al. 2011a	Concomitant use of Non-steroidal Anti-Inflammatory Drugs (NSAIDs)/Aspirin, Selective Serotonin Reuptake Inhibitors (SSRIs) and gastroprotective drugs	Residents of long-term care wards (mean age 81.3±10.9 years) in Helsinki (n=1 087)	Drug-use data: medication administration charts. Diagnoses: medical charts Mortality: central registers 2003	Prevalence and factors associated with concomitant SSRI/NSAID use To investigate the use of gastroprotective drugs among concomitant SSRI/NSAID (including aspirin) users
Bell et al. 2011b	Antiepileptics	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093) and their matched comparisons without Alzheimer's disease (n=28 093)	Finnish National Prescription Register maintained by Social Insurance Institution of Finland MEDALZ-2005 Study[5)], Kuopio, 2005	National pattern of anti-epileptic drug use among persons with and without Alzheimer's disease
Bell et al. 2011c	Strong opioids	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093) and their matched comparisons without Alzheimer's disease (n=28 093)	Finnish National Prescription Register maintained by Social Insurance Institution of Finland MEDALZ-2005 Study[5)], Kuopio, 2005	National pattern of strong opioid use among persons with and without Alzheimer's disease

Desplenter et al. 2011	Psychotropic drugs (anxiolytics, hypnotics, sedatives, antidepressants)	Community-dwelling people aged ≥75 years in Kuopio: n=523 (1998); n=700 (2004)	Data on drug use, demographic factors and diagnostics were elicited during patient interviews by a nurse Data from Kuopio 75+[2)] (1998) and GeMS Study[1)] (2004)	Prevalence of psychotropic drug use in 2004 compared to 1998
Gisev et al. 2011	Benzodiazepines and related drugs	Community-dwelling aged ≥65 years in Leppävirta (n=2 224)	Finnish National Prescription Register year 2000 All-cause mortality was assessed after 9 years by using national registers year 2008	Association between the use of benzodiazepines and related drugs and mortality
Kumpula et al. 2011	Anticholinergics	Residents of 53 long-term care wards in Helsinki aged 81.3±10.9 years (n=1 004)	Resident assessment protocols Structured questionnaires Medication administration charts Central national registers 2003	Prevalence and determinants of anticholinergic drug use and the possible association between anticholinergic drug use and mortality
Laitinen et al. 2011	Antipsychotics	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093) and their matched comparisons without Alzheimer's disease (n=28 093)	Finnish Prescription Register maintained by Social Insurance Institution MEDALZ-2005 Study[5)], Kuopio, 2005	National pattern of antipsychotic use among persons with and without Alzheimer's disease
Luukkanen et al. 2011	Drugs with anticholinergic properties (DAPs)	Patients aged ≥70 years in geriatric wards and nursing homes in Helsinki (n=425)	Comprehensive patient assessment by a nurse and experienced geriatricians using a structured extensive questionnaire, medical records 1999–2000	To investigate the use of DAPs in elderly patients with comorbidities To clarify the relationship between the use of DAPs and delirium To study the prognostic significance of DAPs regarding mortality

Puustinen et al. 2011	Central Nervous System (CNS) medications	Home-dwelling aged ≥65 years in Lieto (n=1 196)	Patient interview Clinical examinations by a health centre physician Clinical tests by a trained research nurse Medical records were used to record previous diagnoses 1990–1991	Whether the use of a single CNS medication and the combined use of multiple CNS medications over time are related to the risk of cognitive decline
Rikala et al. 2011	Psychotrophics (antipsychotics, benzodiazepines and antidepressants)	Community-dwelling aged ≥75 years in Kuopio (n=700)	Data on demographics, health status, cognition, functional capacity and drug use gathered by patient interviews by study nurses GeMS Study[1)] 2004 (baseline), 2005–2007 (three annual follow-ups)	Analyze psychotropic drug use over a 3-year period and characterize those individuals most susceptible to persistent and incident use
Taipale et al. 2011a	Sedatives	Community-dwelling aged ≥75 years in Kuopio (n=700)	Drug use data collected during nurse interview GeMS Study[1)] 2004	Factors associated with sedative load
Taipale et al. 2011b	Psychotropics (antipsychotics, antidepressants, antiepileptics, opioids) and sedatives	Community-dwelling aged ≥75 years in Kuopio (n=700)	Drug use data collected during patient interview by a nurse Test of handgrip strength, knee extension strength, the five repeat chair stand test conducted by a physiotherapist GeMS Study[1)] 2004	To investigate if the use of drugs with sedative properties is associated with poorer muscle strength
Teramura-Grönbland et al. 2011	Anticholinergics, Cholinesterase Inhibitors (ChEls)	People aged ≥65 years living in residential care facilities in Helsinki and Espoo (n=1 475)	Medical charts Psychological well-being was assessed using 6 questions 2007	Prevalence of the use of anticholinergic drugs, ChEls, or their combinations and their association with psychological well-being and the association of anticholinergic drugs with individuals psychological well-being

Uusvaara et al. 2011	Drugs with anticholinergic properties (DAPs)	Home-dwelling people aged 75–90 years with stable cardiovascular disease (CVD) in Helsinki (n=400)	A comprehensive clinical assessment by a study nurse and a geriatrician-internist Diagnoses: medical records Medicines: self-report in the mailed questionnaire and bringing the drug packages to the clinic, verification from medical records Mortality: Statistics Finland, hospitals Hospitalizations: National Hospital Discharge Register DEBATE Study[3)] 2000–2003	To evaluate the impact of DAPs on hospitalization and mortality with a mean follow-up of 3.3 years
2012				
Desplenter et al. 2012	Sedatives	Community-dwelling aged ≥75 years (n=700) and institutionalized aged ≥75 years (n=81) in Kuopio	Data on health status, drug use, and sociodemo-graphic factors elicited during annual patient interviews by a nurse GeMS Study[1)] 2004–2007	Change in Mini-Mental State Examination (MMSE) scores (2005–2007) among uses of sedative drugs in 2004 and 2005 (n=139) to non-users of sedative drugs from 2004 to 2007 (n=310)
Gnjidic et al. 2012	Anticholinergics Sedatives	Community-dwelling aged ≥75 years in Kuopio (n=700)	Data on socio-demographic factors (age, sex, and education level), medication use, medical conditions, and functional outcomes collected by a trained nurse GeMS Study[1)] 2004–2007	Relationship between exposure of anticholinergic and sedative medications (Drug Burden Index (DBI)) and functional outcomes
Gisev et al. 2012	Antipsychotics	Community-dwelling aged ≥65 years in Leppävirta (n=2 224)	Finnish National Prescription Register Special Reimbursement Register (diagnostic data) All-cause mortality assessed after 9 years using national registers 2000, 2008	Risk of death associated with antipsychotic use among older adults with a range of comorbidities

Lönnroos et al. 2012	Medications with anticholinergic and sedative effects	Community-dwelling aged ≥75 years in Kuopio (n=339)	Patient interviews Finnish National Prescription and Special Reimbursement Registers National discharge register 2004	Relationship between exposure of anticholinergic and sedative medications (Drug Burden Index (DBI)) and hospitalization over a 1-year period
Taipale et al. 2012a	Sedatives	Community-dwelling aged ≥75 years in Kuopio (n =700)	Demographic, diagnostic and drug use data collected during patient interviews by a nurse Balance and mobility were tested by physiotherapists GeMS Study[1)], 2004	Association between sedative load and balance and mobility
Taipale et al. 2012b	Sedatives	Community-dwelling aged ≥75 years in Kuopio (n=700)	Demographic, diagnostic and drug use data collected during patient interviews by a nurse Mortality: Population Register Centre GeMS Study[1)], 2004–2007	Change in sedative load over time (from 2004 to 2007) and the corresponding risk of death
2013				
Halla-aho et al. 2013	Analgesics	Two random cohorts of home-dwelling people aged ≥75years in Helsinki: 1999: birth cohorts aged 75, 80 and 85 years (n=2 044) 2009: birth cohorts aged 75, 80, 85, 90 and 95 years (n=1 610)	Postal questionnaires 1999 and 2009	Prevalence of musculoskeletal pain and use of analgesics in two random cohorts 10 years apart Patient characteristics associated with potential undertreatment and overtreatment of pain
Lampela et al. 2013	Anticholinergics	Community dwelling aged ≥75 years in Kuopio (n=621, of them 9.3% (n=53) institutionalized)	Standardized interviews, medical records, blood samples, vision, functional capacity, cognition and mood using validated techniques GeMS Study[2)] 2004–2007	To investigate if serum anticholinergic activity assay results and scores from three ranked lists of anticholinergic drugs are associated with anticholinergic adverse drug events

Uusvaara et al. 2013	Drugs with anticholinergic properties (DAPs)	Home-dwelling people aged 70–90 years without clinical dementia but with a history of stable atherosclerotic disease in Helsinki (n=400)	Postal questionnaires: health status (diagnoses and symptoms), current drug treatment (prescribed and OTC), social relationships Medicine use: the postal questionnaires and bringing the drug packages to the clinic, verification from medical records Clinical assessment and laboratory tests DEBATE Study[3)], Helsinki, 2000	The profile of various cognitive functions (e.g., verbal fluency, naming test, MMSE) related to current use of DAPs
2014				
Gnjidic et al. 2014	Anticholinergic and sedative drugs	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093) and their matched comparisons without Alzheimer's disease (n=28 093)	Finnish Prescription Register maintained by Social Insurance Institution MEDALZ-2005 Study[5)], Kuopio, 2005	Relationship between cumulative exposure to anticholinergic and sedative drugs and hospitalization and mortality in people with and without dementia
2015				
Koponen et al. 2015a	Antipsychotics	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093), restricted to persons having their diagnosis in 2005 (n=7 217)	Finnish Prescription Register maintained by Social Insurance Institution MEDALZ-2005 Study[5)], Kuopio, 2005–2009	Duration of antipsychotic use and factors associated with long-term use of antipsychotic (365 days and over) during a 7-year follow-up (The follow-up of antipsychotic use was started three years before AD diagnosis (2003))
Koponen et al. 2015b	Antipsychotics	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093), restricted to persons having their diagnosis in 2005 (n=7 217, mean age 79.4 years)	Finnish Prescription Register maintained by Social Insurance Institution MEDALZ-2005 Study[5)], Kuopio, 2005–2009	To determine the incidence of antipsychotic use in relation to diagnosis of AD

Laitinen et al. 2015	Antidepressants	Community-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=28 093) and their matched pairs without AD (n=28 093), mean age 80 years	Finnish Prescription Register maintained by Social Insurance Institution MEDALZ-2005 Study[5], Kuopio, 2005	To compare antidepressant use among persons with and without AD
Pitkälä et al. 2015	Opioids and other analgesics and psychotropics (antipsychotics, anxiolytics, antidepressants, hypnotics, phenytoin, carbamazepine, oxcarbazepine, valproic acid, pregabalin and gabapentin)	Institutionalized aged ≥65 years; Nursing home residents 2003 (n=1 987) and 2011 (n=1 576) Residents in assisted living facilities 2007 (n=1 377) and 2011 (n=1 586) in Helsinki	Medical charts 2003, 2007, 2011	To investigate the change in prevalence of opioids, other analgesics, and psychotropic medications in institutional settings over a 8-year period
Taipale et al. 2015a	Benzodiatzepines and related drugs	Home-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=24 966) and their matched pairs without AD (n=24 985) extracted from MEDALZ[5] sample. Mean age in both groups 79 years (SD 7)	Finnish Prescription Register maintained by Social Insurance Institution Data from MEDALZ-2005 Study[5], Kuopio 2006–2009	Prevalence of benzodiazepine and related drug use (especially long-term use) and factors associated with the use among individuals with and without AD during 4-year follow-up
Taipale et al. 2015b	Drug combinations increasing bleeding risk among warfarin users	Home-dwelling persons diagnosed with Alzheimer's disease (AD) residing in Finland 31.12.2005 (n=24 966) and their matched pairs without AD (n=24 985) extracted from MEDALZ[5] sample. Mean age in both groups 79 years (SD 7) Of those warfarin users during the study period 2006–2009 were extracted: n=3 385 with AD (mean age 80.4 years), n=4 830 without AD (mean age 80.5 years)	Finnish Prescription Register maintained by Social Insurance Institution Data from MEDALZ-2005 Study[5], Kuopio 2006–2009	Prevalence and predictors of drug combinations increasing bleeding risk among warfarin users with and without Alzheimer's disease

Tiisanoja et al. 2015	Sedatives	Community-dwelling, dentate, non-smoking aged ≥75 (n=158) years extracted from GeMS Study[1])	Patient interviews carried out by a multiprofessional team of 2 trained nurses, 2 trained physiotherapists and 2 physicians specializing in geriatrics Medical records Clinical oral examinations by one of two examining dentists 2004–2005	Relation of sedative load to carious teeth and periodontal pocketing – indication of infectious periodontal disease

DBI (Drug Burden Index)=A tool that measures a person's total exposure to medications with anticholinergic and sedative properties, using the principles of dose response and maximal effect (Hilmer et al. 2007), STAKES=Finnish National Research and Development Centre for Welfare and Health

[1)] GeMS (Geriatric Multidisciplinary Strategy for the Good Care of the Elderly) Study: 1000 randomly selected persons aged ≥75 years (born before 1 November 1928) living in the city of Kuopio, Finland, in November 2003 were invited to participate in the study. These persons were randomized to intervention (i.e., receiving CGA; n=500) and control (i.e., receiving standard care; n=500) groups. The baseline examination was conducted in 2004, with follow-ups performed in 2005, 2006 and 2007. At the beginning of 2004, the City of Kuopio had a population of 88 253 inhabitants, 5615 of whom were aged ≥75 years. The CGA (Comprehensive Geriatric Assessment) included clinical examinations, medication assessment and interventions to improve nutritional state and functional capacity conducted in multidisiplinary team of 2 physicians (trainees in geriatrics), 2 physiotherapists, and 1nutritionist.

[2)] Kuopio 75+ Study: Cohort study that focuses on the clinical epidemiology of diseases, drug use and functional capacity in elderly persons. Community-dwelling age ≥75 years and living in the city of Kuopio, Finland were included in the study (n=4 518). A random sample of 700 persons was drawn from this population on January 1, 1998. A follow-up of survivors was conducted in 2003.

[3)] DEBATE (Drugs and Evidence-Based Medicine in the Elderly) Study: A "real life" cardiovascular prevention randomized controlled trial. Study population (n=400) home-dwelling individuals aged 75 to 90 were retrieved from a random sample of 4,821 subjects aged 75 to 95 and living in Helsinki, Finland. All subjects had a history of stable cardiovascular disease (CVD). No specific exclusion criteria were set because of the "real-life" nature of the study. The study persons were randomized to intervention (throughout clinical and medication assessment) group (n=199) and control (usual care, yearly visit of a study nurse) group (n=201). During the first visit in the clinic, in 2000, all participants underwent thorough clinical assessments performed by the study nurse and a geriatrician–internist. Follow-up time 3.4 years (Strandberg et al. 2006, Uusvaara et al. 2009, 2011 and 2013)

[4)] The apolipoprotein E ε4 allele (APOE4) gene is found in 23% of the general Finnish adult population, and carrier status is a major risk factor for Alzheimer's disease (AD) (Uusvaara et al. 2009)

[5)] MEDALZ-2005 (Medication and Alzheimer's disease) Study: Register-based cohort study including all community-dwelling persons diagnosed with Alzheimer's disease residing in Finland on December 31, 2005 (n=28 093) and their matched comparisons without Alzheimer's disease (n=28 093). Patients with all stages of AD are included in the cohort. Follow-up data was available until the end of 2009.

6.2.2 Articles describing interventions aimed to reduce potentially inappropriate prescribing and medicine use

Ten (13%) of the 75 articles described attempts to reduce DRPs among the aged (Pitkälä et al. 2001, Lampela et al. 2010 and 2013, Rikala et al. 2011, Leikola et al. 2012, Lähteenmäki et al. 2013, Nurminen et al. 2014, Puustinen et al. 2014, Pitkälä et al. 2014, Juola et al. 2015, Table 13) most of which were randomized controlled trials (RCTs) (Pitkälä et al. 2001, Lampela et al. 2010 and 2013, Rikala et al. 2011, Lähteenmäki et al. 2013, Nurminen et al. 2014, Pitkälä et al. 2014, Puustinen et al. 2014, Juola et al. 2015, Table 13). Eight (80%) of the studies were conducted in outpatient care (Pitkälä et al. 2001, Lampela et al. 2010 and 2013, Rikala et al. 2011, Leikola et al. 2012, Lähteenmäki et al. 2013, Nurminen et al. 2014, Puustinen et al. 2014) and two (20%) in long-term care facilities (Pitkälä et al. 2014, Juola et al. 2015). The size of the study population varied from 89 to 700. The studied interventions were: short term tight control conditions of day hospital care (Pitkälä et al. 2001), pharmacist-led CMR (Leikola et al. 2012), medication review as a part of Comprehensive Geriatric Assessment (Lampela et al. 2010 and 2013, Rikala et al. 2010), psychosocial support provided by a physician for sedative withdrawal (Lähteenmäki et al. 2013, Nurminen et al. 2014, Puustinen et al. 2014) and training the nursing staff on harmful medicine use (Pitkälä et al. 2014, Juola et al. 2015).

Table 13. *Summary of Finnish studies reporting interventions to reduce potentially inappropriate prescribing and medicine use (n=10)*

Study	Intervention	Population/healthcare setting	Data source, year	Study objectives
Pitkälä et al. 2001	Short term (2 or 3 days a week during 2-month period) tight control conditions of day hospital care	Home-care patients (n=174; mean age 77 years; range 43–91 years) randomized to the intervention group (day hospital group; n=88) and control group (n=86), Kirkkonummi, Siuntio	Home visit with a patient interview by a home nurse (all medicines including OTC medicines were counted) Data collection year: not mentioned	To what extent it is possible to reduce polypharmacy and simplify drug regimens during short term tight control conditions of day hospital care Follow-up time 10 months after completion of the intervention programme
Lampela et al. 2010	Medication assessment by a physician as a part of Comprehensive Geriatric Assessment (CGA)	Home-dwelling patients aged ≥75 years randomized to the intervention group (CGA group; n=331) and control (standard care) group (n=313), Kuopio	Patient interview and monitoring annually by a trained nurse (medicine information sources; participants and/or relatives, medical records) Study physician's medication assessment in 2004 GeMS study[1)], 2004–2005	Medication changes and their persistence over 1 year
Rikala et al. 2011	Annual (2004–2006) medication assessment conducted as a part of Comprehensive Geriatric Assessment (CGA) by physicians	Community-dwelling aged ≥75 years randomized to the: intervention (CGA) group (n=361) and control (standard care) group (n = 339), Kuopio	Interview and monitoring annually by a trained nurse (medicine information sources; participants and/or relatives, medical records) Study physician's medication assessments 2004 (baseline)–2006 Data on medicine use 2004 (baseline) and three following years (2005–2007) GeMS study[1)], 2004–2007	The effects of an annual medication assessment conducted as a part of a CGA on the prevalence of psychotropic drug use
Leikola et al. 2012	Comprehensive medication review (CMR) by specially trained community pharmacists	Home-dwelling (n=70) and assisted-living (n=51) patients aged ≥65 years from several cities across Finland	CMR case reports by practicing pharmacists undergoing CMR accreditation training 2006–2007	To assess DRPs (categorized according to Pharmaceutical Care Network Europe (PCNE) V5.01 classification) identified and documented by specially trained community pharmacists as a result of CMR. Also the resulting interventions were studied from the documentation.

Lampela et al. 2013	Medication assessment by a physician as a part of Comprehensive Geriatric Assessment (CGA)	Home-dwelling aged ≥75 years with an orthostatic blood pressure test performed at least once during the study period 2004–2007 were divided in intervention (CGA) group (n=365) and control (standard care) group (n=332), Kuopio	Patient interview and monitoring annually by a trained nurse (medicine information sources; participants and/or relatives, medical records) Annual medication assessments by the study physician GeMS study[1)] 2004–2007	Whether the burden of orthostatic hypotension for individual patients and the health care system in general can be reduced by optimizing medication use as a part of comprehensive geriatric assessment CGA
Lähteenmäki et al. 2013	Psychosocial support and use of melatonin as adjuvants in a 1 month withdrawal from long term use of BZDs (temazepam, zopiclone or zolpidem)	Home-dwelling residents aged ≥55 years with primary insomnia who were long-term daily users of BZDs (n=92) were randomized to intervention (melatonin) group (n=46) and control (placebo) group (n=46), Pori	Patient interviews and clinical examinations: Withdrawal symptoms and adverse events were assessed Plasma BZD determination Randomized controlled double-blinded study 2009–2010	Efficacy of psychosocial support and melatonin and placebo as adjuvants in the withdrawal of patients from long-term BZD use Intervention 1 month, follow-up time 5 months
Nurminen et al. 2014	Psychosocial support and use of melatonin as adjuvants in a 1month withdrawal from long term use of BZDs (temazepam, zopiclone or zolpidem)	Home-dwelling residents aged ≥55 years with primary insomnia who were long-term daily users of BZDs (n=92) were randomized to intervention (melatonin) group (n=46) and control (placebo) group (n=46), Pori	Patient interviews and clinical examinations: Handgrip strength and balance measurements Plasma BZD determinations Randomized controlled double-blinded study 2009–2010	Effects of hypnotic withdrawal on handgrip strength and balance during and after long-term use of BZDs Intervention 1 month, follow-up time 5 months
Puustinen et al. 2014	Psychosocial support and use of melatonin as adjuvants in a 1month withdrawal from long term use of BZDs (temazepam, zopiclone or zolpidem)	Home-dwelling residents aged ≥55 years with primary insomnia who were long-term daily users of BZDs (n=92) were randomized to intervention (melatonin) group (n=46) and control (placebo) group (n=46), Pori	Patient interviews and clinical examinations: Attention and psychomotor performance Reaction times Plasma BZD determinations Randomized controlled double-blinded study 2009–2010	Effects of withdrawal from the long-term use of BZDs as hypnotic drugs on cognitive performance Intervention 1 month, follow-up time 5 months

Pitkälä et al. 2014	4 hour interactive training session for nursing staff to identify potentially harmful medications and corresponding adverse drug events	20 wards of assisted living facilities were randomized to those receiving the 4-hour training session and in those receiving no additional training (20 wards were paired into 10 dyads) Residents in 20 wards of the assisted living facilities were ≥65 years (n=227); intervention group (n=118), control group (n=109), Helsinki	Patients' medication administration charts Cognition, nutritional status and HRQoL was assessed using validated techniques by a study nurse Hospitalizations, health and social status and death days from medical records and central registers 2011–2012	To investigate the effect of nurse training on the use of potentially harmful medications (Beers 2003 criteria (Fick et al. 2003), anticholinergics and sedatives) To explore the effect of nurse training on residents' health-related quality of life (HRQoL), health service utilization, and mortality
Juola et al. 2015	4 hour interactive training session for nursing staff to recognize potentially harmful medications and corresponding adverse drug events	20 wards of assisted living facilities were randomized to those receiving the 4-hour training session and in those receiving no additional training (20 wards were paired into 10 dyads) Residents in 20 wards of the assisted living facilities were ≥65 years (n=227); intervention group (n=118), control group (n=109), Helsinki	Cognition (verbal fluency, clock-drawing test) were assessed at baseline and 6 and 12 months by a study nurse Number of falls per resident over the 12-month follow-up were recorded 2011–2012	Whether education of nursing staff, in assisted living facilities, about harmful medication use has effect on the incidence of falls and cognition

BZD=benzodiazepine, HRQoL=Health-Related Quality of Life

[1)] GeMS (Geriatric Multidisciplinary Strategy for the Good Care of the Elderly) Study: 1000 randomly selected persons aged ≥75 years (born before 1 November 1928) living in the city of Kuopio, Finland, in November 2003 were invited to participate in the study. These persons were randomized to intervention (i.e., receiving CGA; n=500) and control (i.e., receiving standard care; n=500) groups. The baseline examination was conducted in 2004, with follow-ups performed in 2005, 2006 and 2007. At the beginning of 2004, the City of Kuopio had a population of 88 253 inhabitants, 5615 of whom were aged ≥75 years. The CGA (Comprehensive Geriatric Assessment) included clinical examinations, medication assessment and interventions to improve nutritional state and functional capacity conducted in multidisciplinary team of 2 physicians (trainees in geriatrics), 2 physiotherapists, and 1 nutritionist.

7 Aims of the study

This PhD study is a part of a larger research programme carried out in the Universities of Helsinki and Turku aiming to search solutions to improve medication safety of the aged. This study consists of 4 substudies (I–IV) which describe development and validation of a Drug-related Problem Risk Assessment Tool (DRP-RAT) for use by practical nurses (PNs) taking care of home-dwelling clients ≥65 years, aiming to involve PNs more systematically in medication risk management of their clients.

The aims of the substudies (I–IV) were:

1) To systematically review the literature on existing criteria that measure inappropriate prescribing in individuals aged 65 years and older (I)
2) To develop and content validate a Drug-related Problem Risk Assessment Tool (DRP-RAT) for use by practical nurses (PNs) taking care of home-dwelling clients aged ≥65 years (II)
3) To evaluate the feasibility of the DRP-RAT among practical nurses in home care (III)
4) To assess the reliability of the medication risk assessments conducted by PNs by using DRP-RAT and to identify clinically most significant DRPs needing action (IV)

8 Materials and methods

The development of the final DRP-RAT consisted of two major phases. First, the development of the draft DRP-RAT (Phase I). Second, validation of the DRP-RAT (Phase II). The validation of the tool included three steps: 1) content validation 2) assessing the feasibility of the content validated tool among PNs and, 3) testing the validity of the tool in clinical practice (Figure 13, Table 14). This study applied both quantitative and qualitative methods (Table 14).

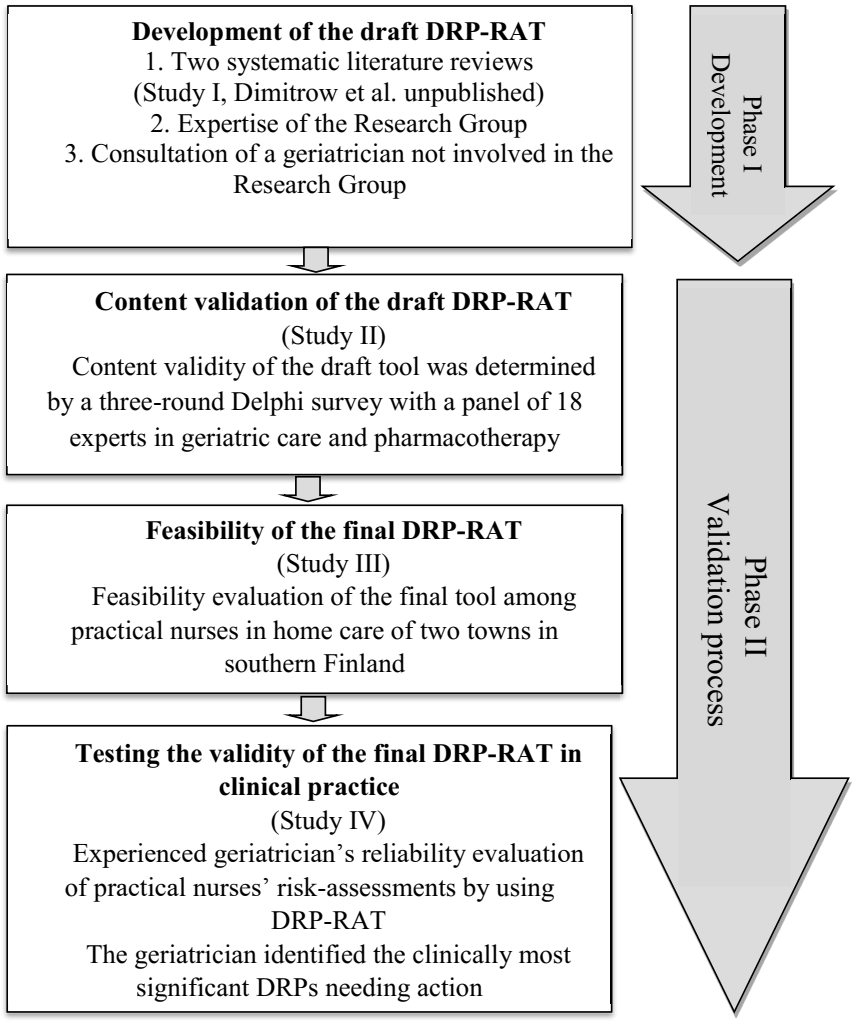

Figure 13 *Outline of the study*

Table 14. *Materials and Methods used in substudies (I—IV)*

STUDY (year)	OBJECTIVES	METHODS	MATERIALS	ANALYSIS
I (2010)	To systematically review the literature on existing criteria that measure inappropriate prescribing in individuals aged 65 years and older. The review focused on the methods employed to develop the criteria and the contents of the criteria with time restriction 1.1.1990–17.6.2010	Systematic literature review	Original English language studies (n=14) describing criteria for measuring inappropriate prescribing in individuals aged 65 and older	Qualitative analysis
II (2010)	To develop and content validate a Drug-related Problem Risk Assessment Tool (DRP-RAT) for use by practical nurses (PNs) taking care of home-dwelling clients ≥65 years	Three-round Delphi survey	Contents of the draft DRP-RAT based on two systematic literature reviews and the expertise of the research group	Quantitative and qualitative analysis
III (2011)	To evaluate the feasibility of the DRP-RAT among PNs in home care	Cross-sectional feasibility study using triangulation	Qualitative and quantitative data collected during training the PNs (n=36) about purpose and use of the DRP-RAT in home care of two towns. Qualitative data: face-to-face discussions i.e., open and structured group discussions and PNs' open comments in the feedback forms Quantitative data: PNs' responses in the DRP-RATs concerning risk medicines listed in the tool, medication lists copied by the PNs	Qualitative content analysis of face-to-face discussions and feedback forms Quantitative analysis of completed DRP-RATs; descriptive statistics (frequencies, percentages, means, standard deviations)
IV (2013)	To assess reliability of medication risk assessments conducted by PNs by using DRP-RAT and to identify clinically most significant DRPs needing action (i.e., validity of the DRP-RAT in clinical practice)	Cross-sectional retrospective study using triangulation	Geriatrician's appraisal of the reliability of medication risk assessments conducted by PNs by using the DRP-RAT. Qualitative and quantitative data collected from study forms including 1) DRP-RAT to be completed by PNs (Phase I of the study), 2) a section to be completed by a geriatrician to assess the reliability of PNs' responses in the DRP-RAT (Phase II of the study) Geriatricians case reports of each patient	Qualitative content analysis of the geriatrician's open comments Quantitative analysis: descriptive statistics (frequencies, percentages, confidence interval for percentages, means, ranges)

8.1 Systematic review of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older (I)

8.1.1 Search strategy

The MEDLINE (Ovid) and PubMed databases were searched from January 1, 1990 to July 17, 2010. The following search terms were used: *inappropriate prescribing, suboptimal prescribing, inappropriate medication, inappropriate practices (Drug Prescriptions), measure, screening tool, criteria, elderly, Beers criteria, and Medication Appropriateness Index (MAI)*. In addition to original research studies, the search covered reviews, systematic reviews, and meta-analyses. The search from these databases was supplemented with a manual search from the reference lists of accepted articles and articles found in authors' files.

8.1.2 Inclusion criteria

Original studies describing criteria for measuring inappropriate prescribing were included in this study if they involved individuals aged 65 and older, were written in English, and described the development methods for the criteria.

8.1.3 Literature search

The search produced 531 potentially relevant publications (I: Figure 1). The titles of these articles were read, and 361 were excluded because the titles showed that the articles were not relevant according to the inclusion criteria. Next, the abstracts of the publications potentially relevant according to their titles were reviewed. In this phase, 138 publications were excluded because the abstracts showed that the articles did not describe the development of the criteria. Twelve publications were excluded because they were duplications. Two researchers read the whole texts of the remaining 20 publications. Both independently excluded the articles not meeting the inclusion criteria. Disagreements were resolved by discussion. In this phase, 12 articles met the inclusion criteria. The manual search from the reference lists of the included 12 articles produced three relevant publications not found in the previous systematic database search, and one additional relevant article was identified in the manual search of the researcher's own bibliographic database. Thus, 16 original studies met the inclusion criteria and described 14 criteria altogether. Two researchers independently classified the nature of the criteria employed (explicit vs implicit).

8.1.4 Outcome measures and data analysis

The original articles were read, and criteria to assess inappropriate prescribing in individuals aged 65 and older and the nature of the criteria (explicit vs implicit), information about the country where the criteria were developed, evidence used to determine the criteria, validation methods, target groups to

which the criteria applied, and the contents of the criteria (which different elements of inappropriate prescribing they measure) were analysed as primary outcomes. The amount of clinical information included in the criteria was analysed as secondary outcomes. The literature review was updated in 2012 covering articles until June 2012 (Dimitrow et al. 2013).

8.2 Delphi survey to validate the content of a tool for assessing risks for drug-related problems in the aged ≥ 65 years (II)

8.2.1 Development process

The DRP-RAT was developed in two major phases (II: Figure 1), namely by 1) developing a draft Tool on the basis of two systematic literature reviews and the clinical expertise of the Research Group, and 2) determining the content validity of the Tool by a three-round Delphi survey.

8.2.1.1 Literature reviews

The literature on existing criteria for assessing inappropriate prescribing in patients aged ≥65 years was systematically reviewed (I). In addition to the above mentioned systematic literature review on potentially inappropriate medications for the aged, another systematic search was conducted searching existing tools designed to screen aged patients at risk for DRPs (Chapter 4.2.3, Dimitrow et al. unpublished). The following search terms were used: *(elderly or aged or ageing) and (medication-related problem or drug-related problem or drug-therapy problem) and (risk) and (screening tool or tool or form).* English language articles published during 1985–2010 were searched in the following databases: Evidence Based Medicine Database, Web of Knowledge, Scopus and Cinahl.

8.2.1.2 Development of the draft DRP-RAT

According to the findings of the first systematic review (I), 1) medicines and medicine classes recognized to pose higher risks for the aged, and 2) potential geriatric-specific ADRs caused by these medicines were identified. Second, according to the findings of the unpublished systematic review that focused on existing age-specific (≥65 years) screening tools (n=6) (Chapter 4.2.3), the most commonly mentioned prognostic indicators for DRPs were listed. The review also revealed some other factors to be considered, particularly the structure of the tool and focusing the screening on potentially harmful ADRs instead of producing a long list of problematic medicines (Pit et al. 2008). Both of these systematic literature reviews' findings were integrated into the draft Tool. Our Research Group's clinical experience was used in this phase, as well as that of an experienced geriatrician who was not a member of the Research Group.

8.2.2 Content validation of the DRP-RAT

8.2.2.1 Delphi method

The Delphi method is a systematic technique for formulating a group judgment concerning subject matter for which the information is incomplete or lacking entirely (Dalkey and Helmer 1962, Campbell and Cantrill 2001). Its validity relies on a panel of experts having been carefully selected, that their individual judgements be provided independently and anonymously via questionnaires in two or more rounds, and that there be aggregated feedback between rounds.

Face validity of the presented DRP risk assessment items of the draft DRP-RAT were assessed using 1-round pilot Delphi survey with a panel of 6 pharmacists accredited for CMR (Leikola et al. 2009, Leikola 2012). Contents of the draft DRP-RAT was validated using a three-round Delphi survey with a panel of 18 experts in geriatric care and pharmacotherapy (11 physicians, 4 nurses and 3 pharmacists) via software called eDelfoi (Metodix 2010).

During the first and the second Delphi rounds, the panelists rated the suitability of the presented items in assessing risks for DRPs in the aged ≥65 years. An agreement by ≥80% of the panel on an item was determined. Round one also included a final open-ended question: *If you think that the draft risk assessment tool ignores some essential aspects of medication risks in routine community clinical practice, please identify each of them*. During the third Delphi round, the panelists rated the importance of the items in final DRP-RAT using rating scale 5 (important) – 1 (unimportant).

Before each Delphi round (pilot and actual rounds), it was stressed to the panelists that the final Tool was meant to be administered by PNs and that the panelists should consider a typical PN's ability to assess the items in clinical practice. The panelists' guidance also emphasized the goal of developing a tool which 1) focuses on the most important predictors for DRPs in the aged, 2) is easy to use in the time-constraints of routine practice, and 3) requires only modest training for PNs.

8.3 Feasibility of the DRP-RAT among practical nurses (III)

Feasibility of the final DRP-RAT among PNs (i.e., PNs' ability to reliably review their clients' medications by using the Tool) was assessed in two HC teams from two towns (A and B) in southern Finland (town A approx. 320 HC clients and 60 HC workers; town B approx. 2000 HC clients and 300 HC workers in total). A group of 11 PNs in town A and 25 PNs in town B participated in the study. In both towns, the PNs were trained on the purpose and use of the DRP-RAT and each HC unit's principles in medication management. The training was based pedagogically on constructive learning, applying experiential learning methods and depended on participants' active involvement. The training consisted of a day-long interactive workshop and involved reviewing four self-selected clients' medications by using the Tool (one as a pre-assignment before the workshop day to become familiar with the Tool, and three as post-assignments after the day). Educational content of the training was based on the DRP-RAT. After the training four members of the research group met with health service managers of both towns' HC services to inform them about what was learned about PNs' educational needs and needs to improve medication management processes.

Triangulation, i.e., combination of different methods and data was used to evaluate the feasibility of the Tool (Table 15) (Smith 2002). Quantitative data were gathered from completed post-assignments in town B (collecting the study materials was pilot-tested in town A) and qualitative data were gathered both in towns A and B from 1) face-to-face discussions, i.e., open and structured group discussions during the workshop day and 2) open questions in the feedback forms. Data obtained from open and group discussions and the feedback forms were combined prior to analysis. Statistical analyses were performed using SPSS Statistical Software 21.0.

8.3.1 Study permission and ethics committee opinion

This was a health service research aiming to assess PNs' ability to reliably review their clients' medications by using the Tool. The HC clients were not provided any care and thus, all patient data were collected and analysed anonymously. Thus, no ethical approval was needed. The study permission was allowed by the health service managers of both towns' HC units.

Table 15. *Outcome measures, data collection and analysis to evaluate the feasibility of the DRP-RAT*

Outcome measure	Description	Data collection	Data analysis	
Time to complete the tool	The time the PNs spent to review one client's medication using the tool	PNs were asked to document the time they spent to complete the post-assignment tool	Minimum and maximum, completing times, means±SD and medians are reported	Quantitative Data gathered from town B
Reliability of the PNs' responses concerning risk medicines listed in the tool[1)] identified to be used by the client	The PNs' responses concerning risk medicines (i.e., amiodarone, carbamazepine, digoxin, diuretics, fluoxetine, lithium, methotrexate, non-steroidal anti-inflammatory drugs, statins, theophylline, warfarin) identified to be used by the client	The information given by the PNs through the tool in the post-assignment phase was verified by comparing PNs' answers about risk medicines with copied medication lists. Later, the verification was double-checked using spot checks	Frequencies and percentages of recognized, not recognized and incorrectly recognized[2)] risk medicines were reported	
PNs' reports about problems to answer the questions in the tool independently without assistance	Challenges met when reviewing individual client's medications using the tool	Data collected via face-to-face discussions, i.e., open and structured group discussions during the workshop day and from the feedback forms	Data were analyzed using standard methods of content analysis (Smith 2002). Items that arose from the data were quantified and grouped into themes based on similarities	Qualitative Data gathered from towns A and B
PNs' opinions about the utility of the Tool in everyday work	a) PNs' view if the tool would help them in their own work (e.g., in regular use) b) ways to use the tool in practice (in everyday work) c) elements that promote or prevent the use of the tool d) suggestions to improve the tool e) unsolicited comments to the developers of the tool and the workshop leaders			

PN=practical nurse, [1)] Medicines that according to studies are recognized to pose higher risks for the aged (I, II) [2)] Recognized, although did not exist in client's medication list

8.4 Validity of the DRP-RAT in clinical practice (IV)

The study was conducted in the four months from September to December 2013 in the HC of Härkätie Health Centre in Lieto (HC clients, n=170; entire HC staff, including nurses and PNs, n=31). Lieto is a municipality with approximately 17 000 inhabitants located in southwestern Finland. Härkätie Health Centre is a primary care unit and part of the public health care system in Finland, which is the dominating health care system covering the entire population through public social insurance (Teperi et al. 2009).

8.4.1 Study design

PNs (n=26) working in HC of the Härkätie Health Centre in Lieto and a clinically experienced physician qualified in geriatrics were recruited for the study. PNs were trained to use the DRP-RAT (III). A data collection form was developed to facilitate the reliability comparisons of PN-conducted medication risk assessments (IV: Table 1). The form included 1) a section to be completed by a PN (the first phase of the study) and 2) a section to be completed by the geriatrician (the second phase of the study). Both the participating PNs and the geriatrician were given oral and written instructions for completing their sections of the form.

8.4.1.1 First phase of the study: DRP Risk Assessments by PNs

The PN's section in the data collection form included 1) DRP-RAT, 2) a short test assessing the client's alcohol use (3 alcohol consumption questions from The Alcohol Use Disorders Identification Test, i.e., AUDIT C) (Bush et al. 1998, Babor et al. 2001), and 3) space for PN's open comments (IV: Table 1). PNs were trained on the purpose and use of the DRP-RAT and on the HC unit's principles in safe medication management (III, Ministry of Social Affairs and Health 2005).

After a 1-day interactive training the PNs reviewed the medications of 1–3 self-selected clients using the DRP-RAT (III). They were instructed to select for review such clients who were supposed to be at risk of DRPs. They also were asked to print the same client's medication list from the health centre's medical record and to complete an AUDIT C test for alcohol consumption (Bush et al. 1998, Babor et al. 2001). They returned the completed documents to the HC office. Before forwarding the documents to the geriatrician, two researchers checked them to ensure they were fully and appropriately completed.

8.4.1.2 Second phase of the study: DRP risk assessment and medication review by the geriatrician

The geriatrician was asked to review each client's medications using three different methods which differed in the amount of clinical patient information available (IV: Table 1, see also Table 16). When conducting each review the geriatrician was asked to be "blind" to the results of the other reviews for the same client. Based on each of the three reviews and her clinical geriatric expertise, the geriatrician was asked to classify whether the client was "an at-risk patient" (i.e., being at risk for clinically

significant DRPs needing more comprehensive medication review) or "not an at-risk patient". If the geriatrician classified the client as "an at-risk patient" based on Medication Review by Method 1 (DRP-RAT information and medication list) she was asked to tick those PN-identified risk predicting notes in the Tool that she regarded as clinically significant risk factors.

The Medication Review Method 2 was regarded as "gold standard" in this study (Table 16). If the patient was classified as "an at-risk patient" using Method 2, the geriatrician was asked to write an open case report about the identified DRPs and to document the DRPs and their causes according to the Pharmaceutical Care Network Europe (PCNE) classification V6.2 (PCNE 2010, described more detailed in Chapter 2.1.2) on a structured data collection form (the geriatrician had received a short training to use the PCNE classification). Other aspects studied are presented in Table 16.

8.4.1.3 Study permission and ethics committee opinion

Ethical approval for the study was received from the Ethical Board of Southwest Finland. The HC clients gave a written informed consent to participate in the study. The study permission was received from the health service manager of Härkätie HC unit.

Table 16. *Aspects studied and methods used for data analysis in determining the DRP Risk Assessment Tool's ability to provide reliable clinical patient information to assist the physician in clinical decision making*

Aspects Studied	Data analysis
The DRP-RAT's ability to assist in identifying older HC clients at risk of clinically significant DRPs **Medication reviews conducted by the geriatrician** (were performed without direct patient contact): **Method 1:** Medication Review based on the DRP-RAT with Audit C completed by the PNs and the medication lists printed from the health centre's medical records **Method 2** (usual care in health centre in cases the physician does not meet the patient)**:** Review based on the health centre's medical records ("gold standard"[1)] of this study) Medical records encompass the following patient data a) visits in health centre, b) clinical examinations (health status, anamnesis, conclusions), c) medication lists, d) laboratory test results, e) hospitalizations, f) HC workers' open comments about their home visits **Method 3:** Review based on Methods 1 and 2 together = all client information available	Frequencies and percentages (95% CI) of the identified "at-risk patients" resulting from each Medication Review Method were reported
Geriatrician's evaluation about the validity of the PNs' recommendations for action to resolve potential DRPs listed in the DRP-RAT	Frequencies and percentages of "valid" and "invalid" recommendations were reported. Results of qualitative analysis of the geriatrician's justifications were reported
Geriatrician's assessment of the DRP-RAT's ability to provide clinically important and timely patient information for clinical decision making	Frequencies and percentages of "yes", "no" and "some additional information" were reported. Results of qualitative analysis of the geriatrician's justifications were reported
Relevance of the questions in the DRP-RAT i.e., prevalence of the DRP risk predicting notes reported by the PNs in the completed DRP-RATs in the study sample	Frequencies and percentages of the risk predicting notes on each question of the Tool were reported
Clinical significance of potential DRPs reported by PNs confirmed by an experienced geriatrician. Significance was determined as follows; the more often the geriatrician evaluated the PNs' DRP risk predicting note in the Tool as a risk factor (i.e., those PNs' risk predicting notes in the Tool that the geriatrician had ticked in order to be risk factors during Medication Review Method 1) the more important the question is	Frequencies of the PN's positive risk predicting notes that the geriatrician evaluated as clinically significant risk factors needing action
DRPs and their potential causes in the study sample documented by the geriatrician and the associated drugs or drug groups using Medication Review Method 2. Geriatrician's case reports of each patient and the PCNE -classification V6.2 done by the geriatrician were analysed. (Two researchers independently double-checked the geriatrician's PCNE-classifications by comparing the case reports and the PCNE-classifications. Obscurities were resolved by discussion)	The documented DRPs, causes of DRPs and the associated drugs or drug groups are reported
Time the geriatrician spent reviewing one client's medication using the DRP-RAT	Time scale, the mean time the geriatrician spent reviewing one client's medication with the Tool are reported

[1)] In normal practice, physicians working in health centre are often forced to make decisions concerning their HC patient's medication without personal patient contact but relying only on a health centre's medical records
AUDIT-C=3 alcohol consumption questions from The Alcohol Use Disorders Identification Test (Bush et al. 1998, Babor et al. 2007)
DRP-RAT=Drug-related Problem Risk Assessment Tool (II), PCNE=Pharmaceutical Care Network Europe (PCNE 2010)

9 Results

9.1 Systematic review of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older (I)

9.1.1 Retrieved criteria

Researchers in the United States were early developers of the criteria; the first criteria being developed in the early 1990s (Beers et al. 1991, Hanlon et al. 1992, Lipton et al. 1993, I: Table 1, Table 17). In Europe, the first consensus-validated criteria were developed in France more than a decade later (Laroche et al. 2007). Ten (71%) of the 14 criteria found in the literature search were explicit (Beers et al. 1991, Beers 1997, McLeod et al. 1997, Naugler et al. 2000, Zahn et al. 2001, Fick et al. 2003, Laroche et al. 2007, Gallagher et al. 2008, Rognstad et al. 2009, Maio et al. 2010), three (21%) were implicit (Hanlon et al. 1992, Lipton et al. 1993, Jeffery et al. 1999), and one contained explicit and implicit criteria (Basger et al. 2008). Most explicit criteria have been validated using consensus methods (Beers et al. 1991, Beers 1997, McLeod et al. 1997, Zahn et al. 2001, Fick et al. 2003, Laroche et al. 2007, Gallagher et al. 2008, Rognstad et al. 2009, Maio et al. 2010). All implicit criteria were validated using patient medical records (Hanlon et al. 1992, Lipton et al. 1993, Jeffery et al. 1999). Target groups, basis of the criteria, development methods and description of the contents of the criteria are presented in Table 17.

Beers criteria and its updates are the most well-known and widely used criteria (Beers et al. 1991, Beers 1997, Fick et al. 2003, AGS 2012, AGS 2015). The most recent update of the Beers criteria was published in 2015 by the American Geriatrics Society (AGS 2015). Most explicit criteria, even the newest ones, have utilized Beers criteria and/or its updates as a basis of the criteria (Figure 14). Also exceptions exist: the Irish STOPP and START criteria was based on evidence-based literature and experience of the investigators (Gallagher et al. 2008). This two-part tool takes into account both inappropriate prescribing and underprescribing among the aged 65 years and older. Due to expanding therapeutic evidence an update of the criteria was published in 2015 (O'Mahony et al. 2015). In Australia, Basger and colleagues (2008) developed their criteria based on the most frequent medications prescribed to Australians and the most frequent medical conditions for which older Australians consult medical practitioners. Australian indicators were updated and validated in 2012 (Basger et al. 2012).

9.1.2 Contents of the criteria

Most criteria measure pharmacological appropriateness of prescribed medicines (Dimitrow et al. 2013). The Australian Tool (Basger et al. 2008 and 2012) and MAI (Hanlon et al. 1992) goes somewhat beyond pharmacological aspects assessing also risks related to the medication use process: (i.e., MAI advices to takes into account practical directions (Hanlon et al. 1992), while the Australian Tool recommends monitoring the effects of medication and laboratory values (e.g., blood pressure, pain, itch or discomfort that interferes with daily activities, international normalized ratio (INR),

creatinine clearance) and, to offer smoking cessation options with certain diseases (Basger et al. 2008 and 2012).

The majority of the instruments represent a quantification of *misprescribing* (Dimitrow et al. 2013). They list potentially inappropriate medications (e.g., anticholinergics, sedatives, neuroleptics, nonsteroidal anti-inflammatory drugs, long-acting sulfonylureas), most common harmful drug-drug and drug-disease interactions and potential geriatric-specific adverse effects related to them. They also describe doses and durations of medications that should not be exceeded. Six criteria concern *overprescribing* (Hanlon et al. 1992, Lipton et al. 1993, Basger et al. 2008, and 2012, Laroche et al. 2007, Gallagher et al. 2008, Rognstad et al 2009). Three of the 14 criteria concern *underprescribing* (Jeffery et al. 1999, Gallagher et al. 2008, Basger et al. 2008), two of them being particularly developed for detecting underprescribing (Jeffery et al. 1999, Gallagher et al. 2008). Through time, explicit criteria have evolved more comprehensive and thus, their use requires more clinical patient data. For example, Beers 1991 (Beers et al. 1991) criteria list only PIMs, while the recent update (AGS 2015) includes PIMs, drug-disease and drug-syndrome PIMs, drugs to be used with caution, drug-drug interactions and PIMs based on kidney function.

Table 17. *Studies on development and validation of prescribing criteria to evaluate the appropriateness of drug treatment in the aged (I: Table 1)*

Criteria, publication year, country	Target group	Criteria based on	Content validity of the criteria defined by	Content of the criteria and the amount of clinical patient information included in the criteria
1. Instruments based on explicit criteria (n=10)				
1.1 Beers criteria and instruments based on Beers criteria (n=9)				
Beers 1991 criteria (US) (Beers et al. 2001)	Nursing home residents aged ≥65 years	Literature (published 1979–1990 in English)	Two-round written survey based on Delphi method with 13 nationally or internationally recognized experts from US and Canada (expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, general clinical geriatrics and long-term care)	**30 criteria statements** ** (19 criteria describing medications or medication classes that generally should be avoided, 11 criteria describing doses, frequencies or durations that should not be exceeded)
Beers 1997 criteria (US) (Beers 1997)	General (ambulatory) population aged ≥65 years	Beers 1991 criteria Literature (published 1990–1995 in English)	Two-round survey (first round: written mail survey, second round: face-to-face full-day meeting) based on Delphi method with 6 nationally recognized experts (expertise in general geriatrics, clinical pharmacology, pharmacoepidemiology, clinical pharmacy and psychopharmacology)	**43 criteria statements classified as having high severity or not** *** (28 criteria describing potentially inappropriate medications, 15 diseases or conditions and medications to be avoided in these conditions)
Beers 2003 criteria (US) Fick et al. 2003	Persons aged ≥65 years	Beers 1997 criteria Literature (published 1994–2000 in English)	Three-round survey (first round: mail survey, second round: face-to-face meeting, third round: mail survey) based on Delphi method with 12 nationally or internationally recognized experts from US (expertise in psychopharmacology, pharmacoepiodemiology, clinical geriatric pharmacology and clinical geriatric medicine)	**68 criteria statements classified as having high or low severity***** (48 criteria describing potentially inappropriate medications, 20 diseases or conditions and medications to be avoided in these conditions)
Zhan criteria 2001 (US) Zahn et al. 2001	General (ambulatory) population aged ≥65 years	A subset of 33 drugs from Beers 1997 criteria (drugs potentially inappropriate irrespective of dose, frequency of administration, or duration of the therapy)	Two-round survey (first round: panelist familiarized themselves with the literature of the subject and independently classified the 33 drugs, second round: conducted via conference call) based on Delphi method with 7 experts (5 geriatricians, 1 pharmacoepidemiologist and 1 pharmacist)	**Classification of the 33 drugs** *** (11 drugs that should always be avoided, 8 drugs that are rarely appropriate, 14 drugs that have some indications for use in an elderly population)

McLeod criteria 1997 (Canada) McLeod et al. 2007	Persons aged ≥65 years	Beers 1991 criteria Literature (not defined exactly in the article) Canada's national drug formularies	Two-round mail survey based on Delphi method with 32 experts (7 clinical pharmacologists, 9 geriatricians, 8 family practitioners and 8 pharmacists)	**38 inappropriate high-risk practices in prescribing grouped into 4 categories with recommendations of alternative therapy***** (18 practices involving drugs generally contraindicated for elderly people, 16 practices involving a drug-disease interaction, 4 practices involving drug-drug interaction)
IPET 2000 (Canada) (Naugler et al. 2007)	Persons aged ≥70 years	McLeod criteria applied to 361 inpatient charts	Not validated (items of MacLeod criteria were validated)	**14 inappropriate practices in prescribing ***** (10 drug-disease interactions, 2 inappropriate medication classes, 2 criteria comprising recommendations for duration of drug therapy)
French criteria 2007 (France) Laroche et al. 2007	Persons aged ≥75 years	Beers criteria (1991,1997, 2003) McLeod criteria Criteria adapted to French practice (derived from the Beers 1997 criteria) Guidelines of the French Medicine Agency	Two-round mail survey based on Delphi method with 15 experts (5 geriatricians, 5 pharmacologists, 2 pharmacists, 2 general practitioners, 1 pharmacoepidemiologist)	**34 inappropriate practices in prescribing with recommendations of alternative therapies***** (29 medications or medication classes that should be avoided, 5 drug-disease interactions)
NORGEP 2009 (Norway) Rognstad et al. 2009	Persons aged ≥70 years in general practice	Beers criteria (1991,1997, 2003) Swedish recommendations (Socialstyrelsen 2003) Recent evidence from literature (published 1996–2008) Clinical experience of the investigators	Three-round mail survey based on Delphi method with 47 experts (14 clinical pharmacologists, 17 geriatricians, 16 general practitioners)	**36 criteria for pharmacologically inappropriate prescribing in general practice*** (21 criteria concerning single drugs and dosages, 15 criteria concerning drug combinations to be avoided)

Italian criteria 2010 (Italy) Maio et al. 2010	Persons aged ≥65 years	Beers 2003 criteria (drugs that should generally be avoided in the aged) Panelists were invited to add additional medications to the initial list	A Nominal Group Technique (Jones and Hunter 1995) with four iterations (first: face-to-face meeting, second: web-based survey questionnaire, third: results of the second round were anonymously shared with the panel, fourth: face-to-face meeting) using a panel of 9 experts (3 general practitioners, 1 geriatrician, 1 clinical pharmacist, 2 psychiatrists, 1 cardiologist, 1 director of long-term care facilities)	**23 reimbursed drugs classified in three categories***** (17 drugs that should always be avoided, 3 drugs that are rarely appropriate, 3 drugs that have some indications for use in an elderly population)
1.2. Instruments not based on Beers criteria (n=1)				
STOPP and START 2008 (Ireland) Gallagher et al. 2008	Persons aged ≥65 years	Evidence based literature (not defined exactly in the article) Clinical experience of the investigators	Two-round mail survey based on Delphi method (Dalkey and Helmer 1963) with 18 experts (9 teaching hospital consultants in geriatric medicine, 3 clinical pharmacologists, 1 old age psychiatry, 2 senior academic primary care physicians and 3 senior hospital pharmacists with interest in geriatric pharmacotherapy)	**STOPP: 65 criteria focusing on prevalent problems associated with commonly prescribed medicines in the aged arranged according to physiological systems** **** (42 criteria concerning avoidance of medications in certain disease states or conditions, 4 criteria concerning specific drug combinations to be avoided, 12 criteria concerning duration of drug therapies, 2 criteria concerning doses, 3 criteria concerning avoidance of prescribing without indication, 2 criteria concerning need of additional therapy) **START: 22 evidence-based explicit prescribing indicators for common diseases in aged people******
2. Instruments based on implicit criteria (n=3)				
MAI [1)] 1992 (Hanlon et al. 1992) Summated MAI [2)] 1994 (US) (Samsa et al. 1994)	Developed among persons aged ≥65 years, but use not restricted to older adults	Literature (Medline and manual search) published 1982–1990 Clinical experience of a clinical pharmacist and an internist geriatrician	*MAI*: convenience sample of 10 academic health care professionals judged MAI items to be "definitely important" or "moderately important", thus providing an independent validation of their suitability *Summated MAI*: applying summated MAI to 105 medications prescribed to 10 elderly veterans. The results reflected the putative heterogeneity in prescribing appropriateness among 1644 medications prescribed to 208 elderly veterans in the same clinic	**10 criteria** (indication**,** effectiveness, dosage, correct directions, drug-drug interactions, drug-disease interactions, practical directions, costs, duplication, duration) **worded as questions to assess the appropriateness of each prescribed drug with instructions for use and operational definitions for each criterion********

Lipton's criteria [3] 1993 (US) (Lipton et al. 1992)	Persons aged ≥65 years	Six potential drug-therapy problems predetermined by the researches (allergy, dosage, duration, schedule, duplication, drug-drug interactions i.e., problems that were not examined rigorously before)	Content validity was established over five meetings of a review panel (1 physician chairperson, 2 pharmacists, 4 physicians); panel discussions, consultation with authoritative compendia, reviewing pilot cases: individual presentations, group review and discussion of the cases, group feedback, applying the instrument to the assessment of actual cases (236 geriatric outpatients)	**6 explicit drug-therapy problem categories** (allergy, dosage (under- or overdosage), schedule (frequency of administration), appropriateness (no indication, less-than-optimal choice of a drug), drug-drug interaction, unnecessary therapeutic duplication) **with definitions and examples the assessment of which requires implicit judgement********
AOU 1999 (US) (Jeffery et al. 1999)	Persons aged ≥65 years	Lipton's methodology[3], to assess omitted but necessary drug therapies for chronic conditions (assessment of medications, laboratory data and diagnoses)	Validity demonstrated in a small case study (n=23, age in years 69,1±15,5) in a long term facility	**A method of assessing the omitted but necessary drug therapies in chronic conditions** ****** (the evaluator compares the list of chronic medical conditions to the prescribed drugs); ratings for each disease or condition: A= no omission, B=marginal omission, C=omission
3. Instruments based on explicit and implicit criteria (n=1)				
3.1. Instruments not based on Beers criteria (n=1)				
Inappropriate Medication Use and Prescribing Indicators Tool 2008 (Australia) (Basger et al. 2008)	Persons aged ≥65 years	Recent Australian literature Most frequent Australian Pharmaceuticals Benefits Scheme (PBS) medications prescribed to Australians in 2006 Most common medical conditions for which Australians 65 years and older consult medical practitioners	Not validated	**45 explicit and 3 implicit prescribing indicators******* (18 criteria concerning avoidance of medications in certain disease states or conditions, 19 concerning recommended treatment in certain disease states or conditions, 4 concerning medication monitoring, 3 concerning specific drug interactions and 1 asking about the presence of any drug interactions, 1 asking about any changes in medication in the previous 90 days, 1 concerning smoking and 1 vaccination status

AOU=Assessment of Underutilization of Medication, MAI=Medication Appropriateness Index, NORGEP=Norwegian General Practice, IPET=Improving Prescribing in The Elderly Tool, RCT=Randomized Controlled Trial, STOPP (Screening Tool of Older Person`s Prescription) and START (Screening Tool to Alert doctors to the Right Treatment), US=United States

* - ****** (* = no clinical patient information, ****** = best available clinical patient information)

[1] Developed as a part of randomized controlled health services research trial (participants: outpatients aged 65 years and older) (Hanlon et al. 1996)

[2] Developed to enhance the MAI's (Hanlon et al. 1992) utility by generating a scoring system that produces a single MAI score per medication based on the importance of the item

[3] Developed as a part of randomized controlled health service research trial (participants: outpatients aged 65 years and older) (Lipton et al. 1992)

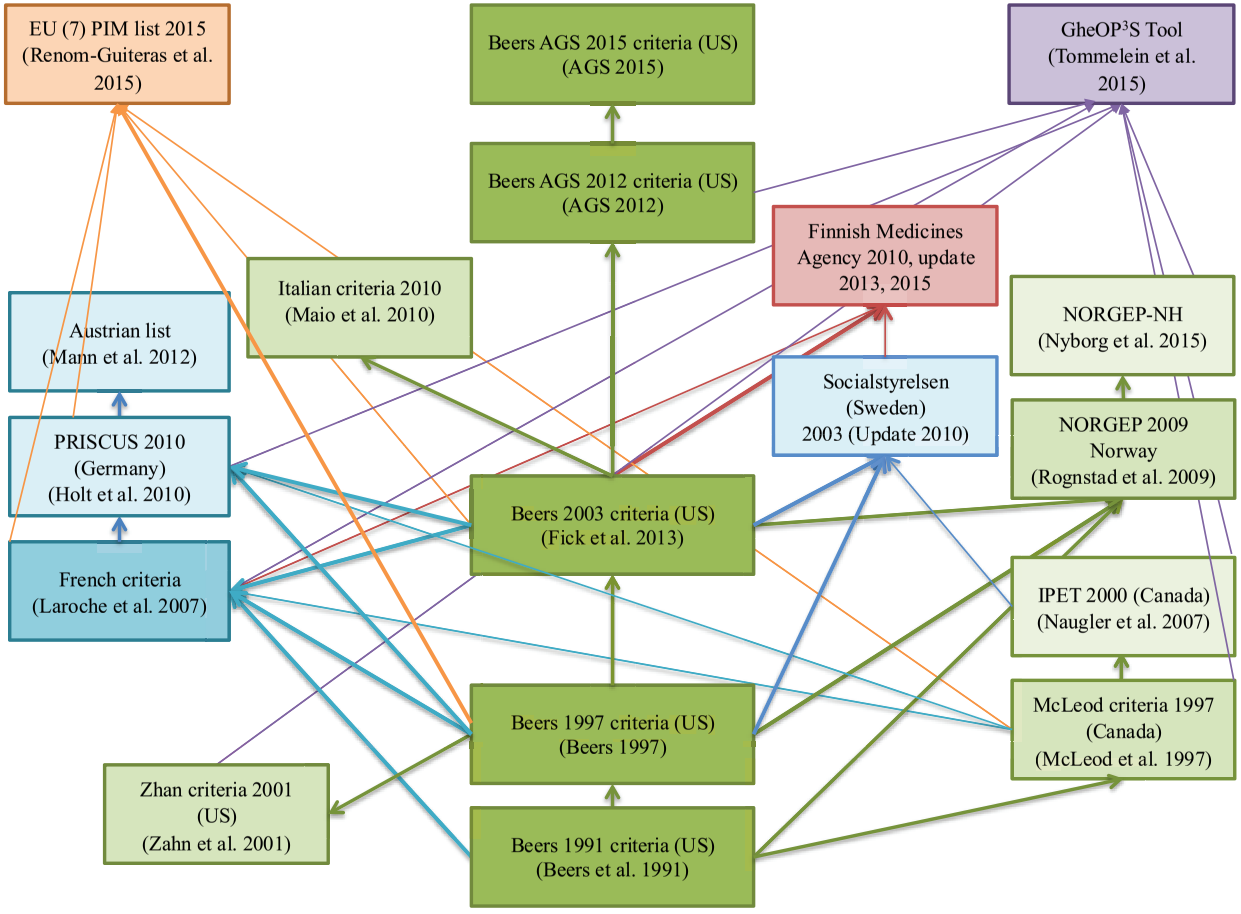

Figure 14 *Most explicit criteria have utilized Beers criteria and/or its updates as a basis of the criteria*

9.2 Delphi survey to validate the content of a tool for assessing risks for drug-related problems in the aged ≥65 years (II)

9.2.1 Results of the Delphi rounds

Expert panelists achieved consensus on 48 of 102 (47%) items (Figure 15, II: Figure 1). In addition to these 48 consensus items, 11 items were retained according to the research group's judgement, resulting in the 59-item final DRP-RAT (each individual item of the final tool's multicomponent items are discussed here as items (II: Table 1). Outline of the development and validation process of the DRP-RAT and results of the Delphi rounds are illustrated in Figure 15 (II: Figure 1).

9.2.1.1 Contents of the final DRP-RAT

The final version of the tool consists of four main sections: 1) Basic Client Data 2) Potential Risks for DRPs in Medication Use, 3) Characteristics of the Client's Care and Adherence, and 4) Recommendations for Actions to Resolve DRPs (Appendix, II: Table 1).

Section 1 (Basic Client Data) focuses on basic client demographic data (age, gender, living alone). It also includes an indicator of whether the client has an up-to-date medication card/list and who administers the client's medications.

Section 2 (Potential Risks for DRPs in Medication Use, 10 main items) focuses on symptoms potentially suggestive of ADRs, use of high-risk medicines and risks posed by polypharmacy. It also includes items of initiation of a new medication, and concomitant use of nonprescription medicines or vitamins with prescription medicines.

Section 3 (Characteristics of the Client's Care and Adherence, 8 main items) includes information about the client's health, adherence to their therapeutic regimen and involvement in one's care, the health care setting, health care units recently visited by the client, and the number of care-taking physicians.

Section 4 (Recommendations for Actions to Resolve DRPs) encompasses seven interventions that PNs can recommend for resolving potential DRPs for those at risk. The PNs' recommendations need to be based on a risk assessment resulting from the information gathered by using the DRP-RAT.

9.2.1.2 Importance of the items in the final DRP-RAT for predicting DRP risks

The panelists of the third Delphi round (n=16) ranked two items as the most important for predicting DRP risks in the aged: 1) the item indicating whether the client has an up-to-date medication list, and 2) the item assessing the client's adherence to his/her medication. All of the items in the final tool were rated either as important or moderately important in predicting DRP risks for those ≥65 years (Figure 15, II: Table 2).

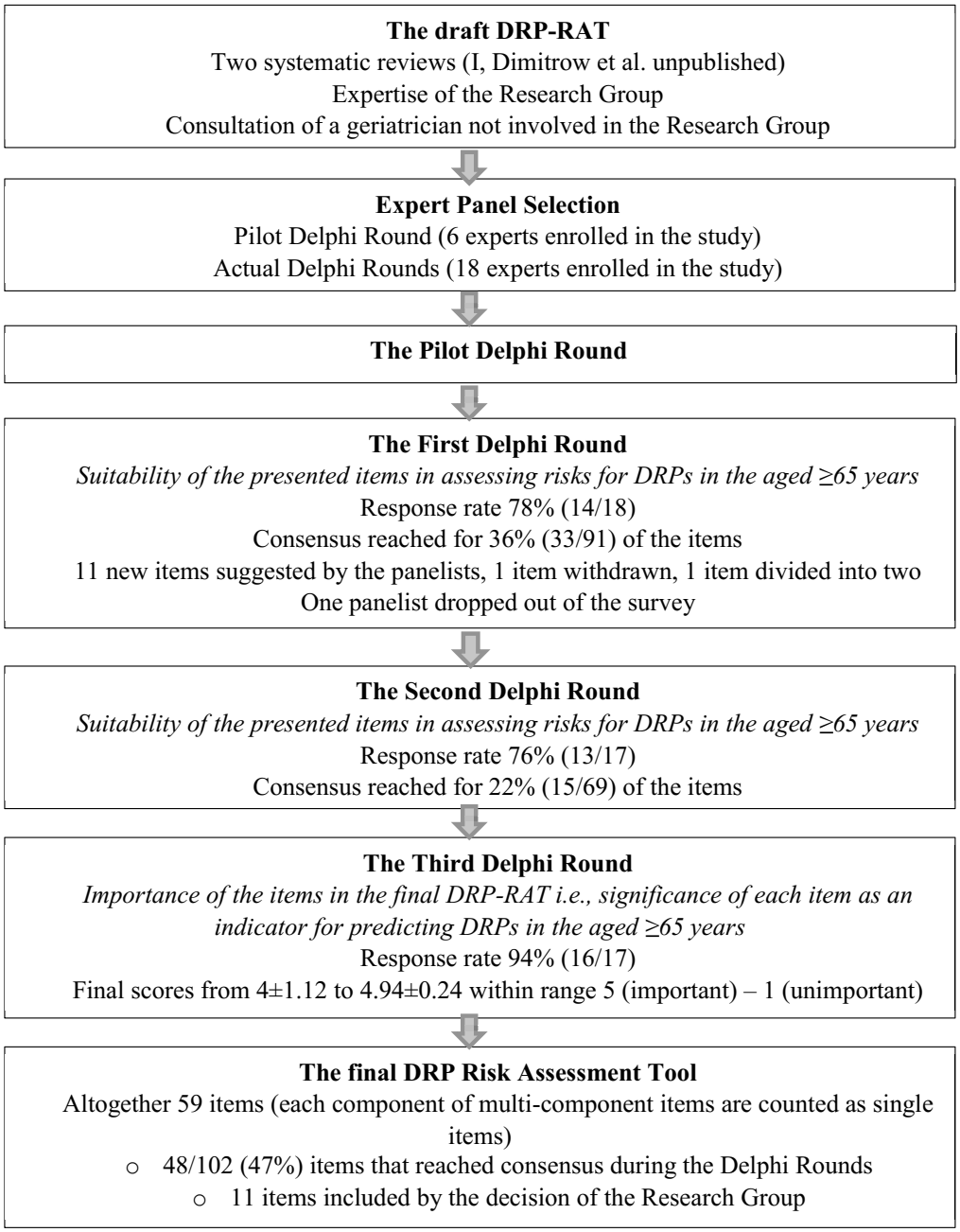

Figure 15 *Outline of the development of the DRP-RAT and validation of its content by Delphi method*

9.3 Feasibility of the DRP-RAT among practical nurses (III)

9.3.1 Quantitative data gathered from town B

9.3.1.1 Time to complete the DRP-RAT and identification of the risk medicines

PNs (n=25) in town B returned altogether 85 medication risk assessments conducted as post-assignments by using DRP-RAT. Of those, 75 included a note of the time the PNs had spent in reviewing one client's medication and 68 included a medication list. The time spent in reviewing one client's medication using the DRP-RAT varied from 10 to 45 minutes (mean 20±8, n=75). The PNs had identified reliably most (96/109; 88%) of the risk medicines used by their clients (Table 18). Non-steroidal anti-inflammatory drugs (NSAIDs), theophylline and diuretics (combination products) were most problematic.

Table 18. *Reliability of the PNs' answers concerning risk medicines listed in the DRP-RAT*

Risk medicines listed in the DRP-RAT	Users total n	Recognized n (%)	Not recognized n (%)	Recognized false[1)]
NSAIDs[2)]	8	3 (38%)	5 (62%)	0
Diuretics	38	32 (84%)	6 (16%)	2
Cholesterol lowering medicines	25	24 (96%)	1 (4%)	3
Amiodarone	0	0 (100%)	0 (0%)	1
Carbamazepine	1	1 (100%)	0 (0%)	1
Digoxin	12	12 (100%)	0 (0%)	2
Fluoxetine	1	1 (100%)	0 (0%)	1
Lithium	0	0 (100%)	0 (0%)	2
Methotrexate	0	0 (100%)	0 (0%)	0
Theofylline	2	1 (50%)	1 (50%)	1
Warfarin	22	22 (100%)	0 (0%)	0
Total	**109**	**96 (88%)**	**13 (12%)**	**13**

[1)] Recognized, although did not exist in client's medication card/list
[2)] Non-steroidal anti-inflammatory drugs

9.3.2 Qualitative data gathered from towns A and B

9.3.2.1 Utility of the DRP-RAT

Response rate of the PN training feedback forms was 64% (23/36; Town A, n=8; Town B, n=15). Of the respondents (n=23), 43% reported that they felt it was easy or quite easy to answer the questions

of Tool. One fourth (26%) of the respondents reported having difficulties in recognizing generic medicines and, that most of the completing time of the DRP-RAT was spent in clarifying generic and trade names. Time constraints, home-care workers' and/or clients' lack of interest to client's pharmacotherapy and short client contacts (i.e., several PNs visit the same client) were the most common barriers to use of the tool. Difficulties in identifying NSAIDs did not arise during the face-to-face discussions nor in the feedback forms. Over a half of the respondents (61%) reported that the DRP-RAT would help in every-day work. One fourth (26%) reported that the Tool would possibly help them. Two PNs (9%) reported that the Tool would not help and one PN (4%) did not comment.

The utility of the tool was also assessed through face-to-face discussions. The PNs had several suggestions how to use the Tool in their daily work but also at organization level (Table 19). They highlighted the importance of teamwork between all professions dealing with pharmacotherapy of the aged to ensure medication safety and thought that the DRP-RAT could serve as a communication aid between different professions. Increasing burden of the PNs making home visits arose several times during the face-to-face discussions. The PNs felt that they often are left alone with the problems of their increasingly old and multimorbid clients. The PNs had several suggestions to improve the tool. Based on those, two items were included in the next version of the DRP-RAT (used in study IV, Appendix): 1) questions about the client's alcohol use (Audit C) and 2) a question: Is there anyone who determines whether the client takes his/her medicines?

It also turned out that there were shortcomings in the medication management process, e.g., the PNs reported that they had no systematic way to detect and report potential ADRs, which were common among their aged clients. The PNs though that the tool would help them to notice and report the most important ADRs and other risks in pharmacotherapy.

9.3.2.2 Overall feedback

Two-thirds of the respondents (65%; n=15/23) to the feedback forms gave positive feedback about the DRP-RAT and the related training program. They responded that the training program was interesting and useful and that they learned a lot about geriatric pharmacotherapy during the program. Many PNs felt that their opinions were taken into account because of the interactivity of the workshop day. They commented that physicians should also be informed about the DRP-RAT. One third of the respondents (35%; n=8/23) did not comment indicating neutral feedback.

9.3.2.3 Feedback to health care managers

The content of the Tool and the interactivity of the training program enabled the PNs to recognize and discuss development needs in the medication management process in HC from their viewpoints. The need for 1) enhanced co-operation with client's care givers and 2) creating a systematic way to monitor and deal with potential DRPs, especially the ADRs, were the most often mentioned development needs. In addition to the above mentioned items, PNs' educational needs concerning medicines (especially NSAIDs and generic names of medicines) were brought to the attention of health care managers in the feedback session.

Table 19. *Practical nurses' opinions about the utility of the DRP-RAT*

Practical nurses' suggestions how to use the Tool
The tool could serve as a communication aid: • An instrument for interprofessional teamwork (PN-nurse-physician-pharmacist) • Promotes co-operation with clients' care givers
The tool gives a reminder: • About the importance of things concerning medication safety • To take notice of the client's total medication • To take more notice on monitoring and reporting possible ADRs e.g., when starting a new medicine • About the problems that maybe have existed, but have not been taken into action (things become concrete when they are written down)
Could be used: • In the account of a new client • When making service and care plans[1)] • During preventive home visits[2)] • When clients are transferred between health care units • When educating new members of a HC team
The Tool helps the PNs to be up-to-date concerning clients' medicines, especially when the medicines are administered by someone else (e.g., automated dose dispensing[3)])
Abbreviations: ADR=Adverse Drug Reaction, PN=Practical Nurse [1)] In Finland, regular HC clients have a valid service and care plan (The Ministry of Social Affairs and Health 2008) The plan is based on an assessment of the client's health status, functional capacity and help needs defined in co-operation with the client (and/or client's family or friends) and HC workers [2)] Legislative visits aiming to support wellbeing, health and functional capacity and to provide information about municipality's services for the elderly aiming to help older people to continue living at home (The Ministry of Social Affairs and Health 2008 and 2012) [3)] Medicines are packed in unit-dose bags according to administration times (Sinnemäki et al. 2013 and 2014)

9.4 Reliability of the medication risk assessments conducted by PNs by using DRP-RAT and the clinically most significant DRPs needing action (IV)

The PNs (n=26) returned a total of 46 completed DRP Risk Assessments including Audit C assessments for alcohol consumption (mean 1.8 assessments per PN). The mean age of the home-care clients whose medications the PNs reviewed (n=46), was 83 (range 64–96) years. Most of them (65%) were women and lived alone (91%). They had a mean of 9.5 (range 4–15) prescription drugs in regular use, mean 2.9 (range 0–12) as needed prescription drugs and mean 0.2 (range 0–1) prescription drugs taken as a course. Twelve clients (26%) had used Over-the-Counter (OTC)-medications for two weeks prior to the risk assessment.

9.4.1 The Tool's ability to assist in identifying older HC clients at risk of clinically significant DRPs

Of the 46 clients, the geriatrician reviewed altogether 45 clients' medications using all three methods (one client was excluded as he regularly visited a specialist and tertiary care university hospital). Figure 16 shows the results of the medication reviews. Compared to the "gold standard" (Method 2), Method 1 resulted in a false negative rating in 7% (95% CI 1.4–18.3) of the cases (3/45). Using Method 2, the additional data from the health centre's medical records (blood pressure, weight loss, laboratory values) resulted in positive ratings concerning these three cases. The time the geriatrician spent reviewing one client's medicines, using the Tool, varied from 2 to 6 minutes (mean 3.9).

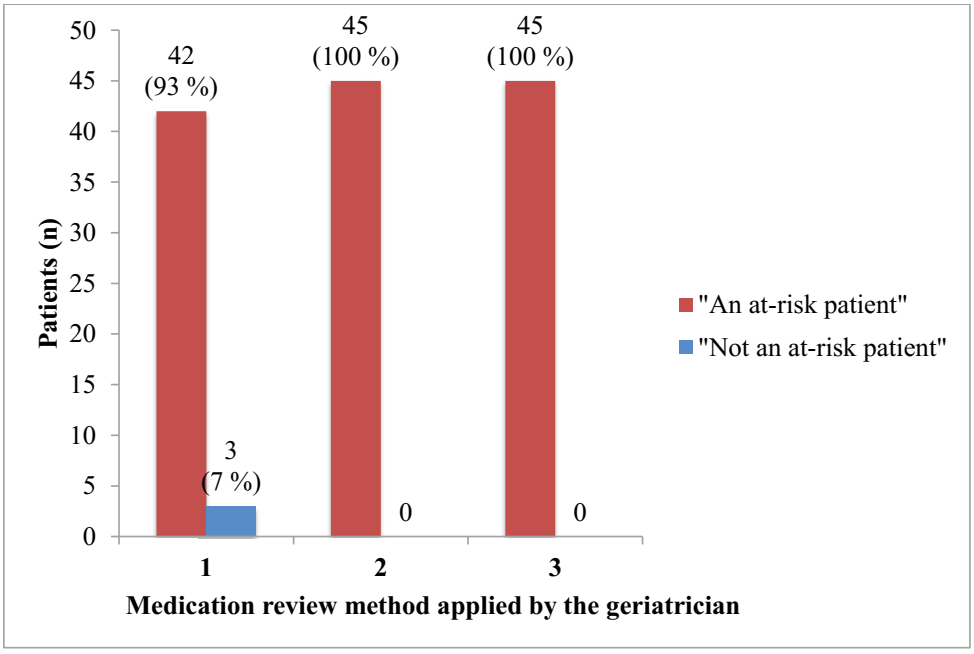

Figure 16 *"At-risk patients" and "not at-risk patients" resulting from three different medication review methods applied by the geriatrician. 1=DRP-RAT and medication list, 2=Health centre's medication records ("gold standard"), 3=Methods 1 and 2 together*

9.4.2 Validity of PNs' recommendations for intervening actions

The PNs had completed the section recommendations for action to resolve potential DRPs in 39 out of 45 (87%) DRP-RATs. A comprehensive medication review was the most commonly recommended action (27/39), followed by automated dose dispensing service (19/39). The geriatrician appraised the recommendations valid in 82% of the cases (32/39).

9.4.3 DRP-RAT's ability to provide clinically important timely patient information for clinical decision making

The geriatrician reported that 87% (39/45) of the medication risk assessments completed by PNs using DRP-RAT provided her with clinically important timely patient information for clinical decision making. Four (9%) of the risk assessments provided some and two (4%) no additional clinically important information.

In 71% (n=32) of the risk assessments the Tool provided the geriatrician with valuable information about symptoms suggestive of ADRs. PNs' notes about medicines prescribed by private practitioners, medicines that clients had not taken although prescribed, and use of herbal products also clarified the client's medication use to the geriatrician. Other important information for clinical decision making were related to the caregiver's concern about the client's medication use, and information about the client's alcohol consumption and adherence.

The geriatrician perceived as a deficiency in the medication risk assessment by DRP-RAT that the Tool lacked information about the patient's health status (e.g., current blood pressure, heart rate, weight, weight changes, bowel motion). However, her experience-based opinion was that the PN-completed Tool, even in its current form without information on client's health status, assisted the physician to focus on the most important DRPs (including the suggested ADRs), i.e., to prepare better for more comprehensive medication reviews.

9.4.4 Prevalence and clinical significance of the risk predicting factors included in DRP-RAT

Most of the risk predicting factors listed in the Tool were prevalent among the study sample, the prevalence varying from 2–91% (IV: Table 3). Over half (60%; n=12) of the risk predicting factors exceeded the prevalence of 20%.

The clinically most significant risk factors for DRPs that the geriatrician prioritized are presented in Table 20. She classified symptoms suggestive of ADRs as the most important indicator for clinically significant DRPs and thus, a reason to conduct a more comprehensive medication review. Among the most significant risk factors were also visiting several practitioners, having more than one fall in the past 12 months prior to the DRP risk assessment and using "high-risk" medicines. Factors related to poor adherence were classified as risk factors in 25% (n=11) of the HC clients. In this study, the number of medicines and the number of medication doses taken were not classified among the most important risk predicting factors (Table 20).

Table 20. *The most important risk predicting factors for DRPs as identified by the geriatrician and their prevalence in the study population*

Risk predicting factor (n=number of PNs' notes (yes or no) on a risk predicting item)	**Prevalence of the risk predicting factors reported by PNs** (n; % of the cases)	**Importance of the questions in identifying risks for clinically significant DRPs conformed by the geriatrician** (n=number of times the geriatrician evaluated the risk predicting factor as a reason for risk; % of the cases)
Has the client had any of the following symptoms in the last 4 weeks? *drowsiness, fatigue, skin rash or itch, dizziness, urination problems, muscle pains, nausea, diarrhea, constipation, dizziness when getting up, recurrent falls, swellings, memory problems, confusion, visual problems, stiffness, troubles in walking, low blood pressure; systolic pressure under 110 mmHg* (n=44)	40 (yes) (91%)	26 (65%)
Does the client have more than one physician involved in his/her care? (e.g., general practitioners, specialists, private practitioners) (n=44)	22 (yes) (50%)	20 (91%)
Has the client had more than one fall in the past 12 months? (n=44)	18 (yes) (41%)	18 (100%)
Does the client use any of the following medicines (please check the ones used)? *amiodarone, carbamazepine, digoxin, fluoxetine, lithium, methotrexate, theophylline, warfarin* (n=44)	16 (yes) (36%)	14 (88%)
Has the client had troubles in a) remembering to take the medicines? b) following the medicines regimen? c) knowing what his or her medicines are used for? d) affording the medicines (i.e., economic problems)? e) opening the drug bottles or packages or managing with medicines related therapeutic devices? (n=44)	30 (yes) (68%)	11 (37%)
Does the client use medicines that a) relieve pain by reducing inflammation (does not apply to paracetamol)? b) elevate the rate of urination (diuretics)? c) are intended to lower the cholesterol level (statins)?) d) the physician does not know about? (n=44)	35 (yes) (80%)	8 (23%)
Have the client's relatives/proxies expressed their concern about the client's medicine use? (n=43)	7 (yes) (16%)	7 (100%)
Has the client started a new medicine in the last 4 weeks? (excluding different brands of the same active incredient) (n=44)	7 (yes) (16%)	6 (86%)

9.4.5 DRPs in the study sample documented by the geriatrician and drugs or drug groups involved in them

9.4.5.1 Drug-related problems and their causes

Using the "gold standard" i.e., Medication Review Method 2 the geriatrician identified altogether 139 potential DRPs (an average of 3.1 per patient, range 1–8).

Over half (53 %; n= 73/139) of the identified DRPs were related to potential adverse reactions (i.e., patient suffers, or will possibly suffer, from an adverse drug event), 34%; n=47/139 were related to treatment effectiveness, i.e., there is a (potential) problem with the (lack of) effect of the pharmacotherapy; and the rest (14%; n=19/139) were related to treatment costs (i.e., the drug treatment is more costly than necessary).

The potential causes of DRPs are presented in Table 21. Two-thirds of the causes (69%; n=96/139) were related to drug selection, 16% (22/139) to treatment duration, 14% (19/139) to dose selection and 1% (2/139) to drug form. Drug groups most commonly involved in these DRPs were drugs for cardiovascular diseases (n=20), hypnotics and sedatives (n=13), drugs for osteoporosis (n=13), Selective Serotonin Reuptake Inhibitors (SSRIs) (n=11) and drugs used for diabetes (n=8).

Table 21. *Potential causes of Drug-related Problems (DRPs) (n=139) in the study population and the associated drugs or drug groups*

(Potential) cause of Drug-related Problem	Home-care clients (n=45) % (n)	Causes of DRPs % (n)	Drugs or drug groups associated (n)
Indication for drug-treatment not noticed	51.1 (23)	20.3 (28)	Ca + vitamin D (n=9), laxatives (n=7), bisphosphonates (n=3), vitamin D (n=2), PPIs (n=2), statins (n=1), folic acid (n=1), low-dose ASA (n=1), local estrogen (n=1), sublingual nitroglycerine (n=1)
Duration of treatment too long	37.8 (17)	15.9 (22)	Hypnotics and sedatives (n=9), PPIs (n=5), folic acid (n=3), systemic antihistamines (n=2), anti-infectives (n=2) (nitrofurantoin; n=1, trimethoprim; n=1), potassium (n=1)
Inappropriate combination of drugs	33.3 (15)	15.9 (22[1)])	Warfarin + SSRI (n=1), warfarin + SSRI + ChEI (n=3), warfarin + SSRI + ASA (n=1), SSRI + ASA (n=3), SSRI + ASA + dipyridamol (n=1), ASA + NSAID + ChEI (n=2), ASA + NSAID + dipyridamol (n=1), paracetamol + carbamazepine (n=1), α-receptor antagonists (tamsulosin) + β-blocker (bisoprolol) (n=1), ACE-inhibitor + potassium-sparing diuretic (n=1)
Inappropriate drug	26.6 (12)	13.8 (19)	Amitriptyline (n=3), theophylline (n=3), diazepam and combination products (n=2), solifenacin (n=2), betahistine (n=2), ibuprofen (n=1), sodium picosulfate (n=1), bulk-laxative (n=1), statins (n=1), SSRI (n=1), tramadol (n=1), trimethoprim (n=1)
No indication for drug	24.4 (11)	10.9 (15)	Oral nitrates (n=7), blood glucose lowering drugs, excluding insulins (n=2), potassium (n=2), allopurinol (n=1), antipsychotics (n=1), sedatives (n=1), tizanidine (n=1)
Drug dose too high	26.6 (12)	10.1 (14)	Blood glucose lowering drugs, including insulins (n=5), statins (n=3), β-blockers (n=2), ASA 250 mg (n=1), furosemide (n=1), paracetamol (n=1), SSRI (n=1)
Inappropriate duplication of therapeutic group or active ingredient or Too many drugs prescribed for indication	20 (9)	7.2 (10)	Loop-diuretic + tiatside-diuretic + AT-blocker (n=1), loop-diuretic + potassium-sparing diuretic (n=1), loop-diuretic + vascular selective Ca-channel blocker + AT-blocker (n=1), tiatside-diuretic + ACE-inhibitor (n=1), loop-diuretic + ACE-inhibitor + β-blocker (n=2), vascular selective Ca-channel blocker + β-blocker + dipyridamol, ASA 25 mg combination product (n=1), (central-acting) α_1-receptor antagonist (prazosin)+ β-blocker + vascular selective Ca-channel blocker (n=1), concomittant use of 3 CNS drugs for sedation (oxazepam, zopiclone, mirtazapine) (n=1), ASA 100 mg + dipyridamol, ASA 25 mg combination product (n=1)
More cost-effective drug available	4.4 (2)	1.4 (2)	Glucosamine (n=2)
Inappropriate drug form	4.4 (2)	1.4 (2)	Long-acting tramadol (n=1), phentanyl plaster (n=1)
Drug dose too low	4.4 (2)	1.4 (2)	Blood pressure medication (n=2)
Dosage regimen too frequent	4.4 (2)	1.4 (2)	Pregabalin (n=1), calcium (n=1)
Deterioration/improvement of disease state requiring dose adjustment	2.2 (1)	0.7 (1)	Metformin (n=1)

[1)] If there are both pharmacokinetic and -dynamic interactions in the drug combination (e.g., warfarin + SSRI + ChEI), it has been counted as two potential causes of DRPs

Abbreviations: ACE=Angiotensin Converting Enzyme, ASA=Acetylsalicylic acid, AT-blocker=Angiotensin II receptor blocker, Ca=Calcium, ChEI=Cholinesterase Inhibitor, CNS=Central Nervous System, DRP=Drug-related Problem, PPI=Proton Pump Inhibitor, SSRI=Selective Serotonin Reuptake Inhibitor

10 Discussion

10.1 DRP-RAT (I–IV)

This dissertation indicates that the DRP-RAT, developed and validated in this PhD study (I–IV), could make it possible to more effectively involve PNs working in HC in medication risk management among home-dwelling aged. Unlike existing nurse-administered risk assessment tools focusing mainly on issues relating to adherence and medication management, the DRP-RAT focuses on the highest priority risks related to the pharmacological effects of the medications but also on factors related to the medication use process. In addition to identifying pharmacotherapeutic risks, the DRP-RAT assists in finding solutions to these problems, which also is a unique feature when the Tool is compared to previous risk assessment tools (Johnson et al. 2005, Pit et al. 2008, Fuller and Watson 2015, Gusdal et al. 2011).

Although PNs are those who most often visit aged HC patients they are ignored from interventions to improve medication safety among the aged both at international (Chapter 4) and national level (Chapters 5 and 6). This PhD study is unique as it aims to involve also the PNs in medication risk management.

This dissertation revealed several improvement needs at systems level in HC organization but also PNs' educational needs related to geriatric pharmacotherapy (III). The study also brought up new information about the highest priority risks that should be focused on in geriatric pharmacotherapy (IV). These risks are related both to pharmacological effects of medication and to medication use process.

10.2 Development of the draft DRP-RAT (I, unpublished)

To ensure a comprehensive content of draft DRP-RAT two systematic literature reviews were conducted (I, Dimitrow et al. 2013, unpublished). The first systematic review about existing criteria measuring inappropriate prescribing among the aged brought out that majority of the existing explicit criteria are consensus validated and based on Beers criteria and their updates (I). It may be discussed if this feature is a shortcoming or an advantage. Lack of new innovation may be missing; the development methods (i.e., consensus methods) and structure and contents of other criteria are quite similar to the Beers criteria, although the drug selection has been modified according to the developing country's drug selection. However, certain basic items originating from Beers criteria have been proved valid through several consensus panels all over the world offering, to some extent, transnational comparability of the process. This may be considered as an advantage.

Each of the reviewed criteria has limitations. The contents of the criteria may be limited as a consequence of the development method. Because of the nature of the Delphi technique (Dalkey and Helmer 1963, Campbell and Cantrill 2001) important items may be dropped if the panelists cannot reach consensus (Fick et al. 2003). The contents of the criteria may also be limited as a consequence of the purpose of the development.

Through time explicit criteria have evolved more comprehensive and thus, their use requires more clinical patient data (Beers 1991, AGS 2015). This reflects the growing knowledge about this research area and thus, growing understanding that applying the criteria in clinical work always require individual clinical judgement. Although the criteria measuring inappropriate prescribing are extremely important they mainly measure the "pharmacological appropriateness on prescribing" and thus, target only a small part of the whole problem (Budnitz et al. 2011). However, DRPs may occur during the whole medication use process (Cipolle et al. 2004, PCNE 2010, Basger et al. 2015). Thus, to complement the first literature review, another systematic review searching existing geriatric specific tools designed to screen aged patients at risk of DRPs was conducted (unpublished, Chapter 4.2.3). The second literature review brought evidence based information and a systems approach to risk assessment. In addition, the research group's clinical experience was utilized in the development of the draft DRP-RAT. Combining the results of these two literature reviews complemented with clinical expertise of the research group assured comprehensive content of the draft DRP-RAT.

10.3 Content validation of the draft DRP-RAT (II)

Developing the draft DRP-RAT followed a rigorously selective process to produce an instrument that could be used by PNs supporting medication management for home-dwelling clients ≥65 years but who have only modest formal training in pharmacotherapy. A three-round Delphi process yielded consensus (≥80 % agreement on an item) on 48 DRP risk assessment items and a final agreement on the resulting 59-item tool.

In addition to indicating potential risks from the pharmacological effects of the medications, particularly ADRs, the DRP-RAT includes measures on risks related to poor adherence and to poor medication management, such as not involving clients and/or their caregivers in care, infrequent follow-ups, and poor coordination of care among the client's health care providers. The importance of adherence and medication management for minimizing DRP risks was confirmed by the Delphi panel experts who gave their final highest importance ratings to items indicating whether the client has a timely medication card/list and whether the client adheres to his/her medication. These indicators, either one or both, are missing or have had a minor role in previous tools that assess DRP risks in the aged (Barenholz Levy 2003, Fuller and Watson 2005, Johnson et al. 2005, Gusdal et al. 2011). Another unique feature of the final DRP-RAT is that, in addition to assisting PNs in identifying home-dwelling aged clients who have or who are at risk for DRPs that require actions, the tool actually guides the selection of such actions. This feature of the tool may increase awareness among PNs and also the aged of options to improve medication safety (e.g., CMR, dose dispensing, consulting an accredited pharmacist).

One third of the individual items in the DRP-RAT that resulted from the Delphi survey are indicators of potentially harmful ADRs. The number of the ADRs is high, even though over half of the initially nominated ADRs (28/46, 61 %) and most of the initially suggested problematic medicines (14/18, 78 %) were excluded during the successive Delphi rounds. This indicates the importance of taking ADRs into account as an integral part of medication use and of identifying ways to identify them early and manage them. The DRP-RAT explicitly guides PNs in the detection of specific symptoms associated with potential ADRs requiring attention. Otherwise, ADRs tend to be underreported among the aged as they may consider the symptoms to be a part of normal aging

(Lampela et al. 2007). It is notable that the list of indicators of potential ADRs covers symptoms that may be caused by PIMs but also symptoms that may be caused by other medicines typically used by aged medicine users i.e., hypoglycemics, blood pressure medications, diuretics. This is a very important feature of the tool, as it is well documented in literature, that few commonly used medications (e.g., warfarin, hypoglycemics) represent as a leading cause of emergency department visits and hospitalizations in the aged (Budnitz et al. 2011). PIMs were implicated only in 1.2% of hospitalizations.

Expert panelists reached consensus on 48 of 102 initial items (47%), which is less than the ratio in several other conceptually similar Delphi surveys reported in the health services' research literature (Cantrill et al. 1998, Morris and Cantrill 2003, Rognstad et al. 2009). The criterion for consensus (80%) to determine attainment of the goal was high (Diamond et al. 2014): consequently, achievement of consensus was low. Therefore, only the most important items for identifying DRP risks in home-dwelling clients ≥65 years were retained in the final DRP-RAT. Furthermore, our Delphi panel comprised physicians, pharmacists, and nurses who are leading experts in geriatric care and pharmacotherapy in Finland. Thus, they should have had the most comprehensive knowledge of typical potentially harmful ADRs and other risks for DRPs which require active management. In order to keep the panelists focused on the DRP-RAT's intended use, it was stressed to them before each Delphi round that the tool was meant to be administered by PNs and they have to consider a PN's ability to evaluate DRP risks for their individual home-dwelling aged clients.

One of the Delphi technique's limitations is that important items may be excluded if the panelists cannot reach consensus (Fick et al. 2003). To avoid such omissions, we retained 11 items in the final DRP-RAT despite their lacking consensus. Based on scientific evidence and our research group's clinical expertise, those items were considered too important for the intended purpose to be excluded. Also, the Delphi panelists rated these retained items as important or moderately important during the third round survey, indicating their endorsement for including these additional 11 items in the final DRP-RAT.

10.4 Assessing the feasibility of the content validated DRP-RAT among PNs (III)

The results indicate that the DRP-RAT is feasible for the PNs and suitable for their skills. The brief training on the content and use of the tool seems to be sufficient for ensuring reliable use of the tool.

HC is teamwork between physicians, nurses and PNs. However, they often are separated from each other as they work to care for the client, the PNs being those who most often visit the client. The PNs felt that they often are left alone with the clients and their pharmacotherapy problems. Thus, they thought that a structured Tool would help them to contact the doctor in acute difficult situations. They also found the Tool to be a useful communication aid to help them to collect and report essential data about the client's pharmacotherapy risks to be discussed with other members of the interdisciplinary HC team (physicians, nurses, PNs). The PNs especially stressed the importance of the Tool's questions assessing symptoms suggestive for ADRs. The structured Tool would also harmonize the information given by several PNs with different communication skills. Previous studies support their opinion; it has been proved that a structured method of communication improves the clarity and

content of interprofessional communication in nursing homes and has the potential to improve nurse and physician work satisfaction (Renz et al. 2013).

10.4.1 Problems that the PNs met when reviewing medications using the DRP-RAT

The DRP-RAT is designed to indicate potential risks from the pharmacological effects of the medications and it also includes measures on risks related to medication management process. Thus, the problems that the PNs met when using the Tool were related to their own skills as well as to the system.

The time scale (10–45 minutes) was wide in completing the Tool as a post-assignment, which may indicate a variation in the skills of the PNs but also a variation in clients' health and complexity of medications. The PNs reported that most of the time required to complete the Tool as a pre-assignment (10–60 minutes, median 30, mean 27±12) was spent in clarifying generic and trade names of medicines. One quarter of PNs reported still having difficulties with generic names when completing the post-assignments although the completing time was shortened significantly (10–45 minutes, median 20, mean 20±8). This indicates that if the Tool is in regular use the completing time may shorten.

Almost half of the PNs reported that they had difficulties with generic names of medicines as they were used to communicating with trade names. Although generic substitution saves both the patients' and society's medicine expenditures, several studies indicate that generic substitution is a risk factor for medication errors, e.g., overdosing (Schwab et al. 2002, Håkonsen et al. 2011, Lobo et al. 2013). In addition, all the extra time spent in clarifying generic names of medicines is subtracted from caring the client. The lack of knowledge concerning risk medicines, especially NSAIDs, is also an issue that must be taken into account when developing continuing education and PN curricula. More focus on NSAIDs must be paid in future trainigs about the purpose and use of the DRP-RAT.

The other problems that the PNs met when using the Tool related more to the HC system than to the skills of the PNs (e.g., short duration of home visits and client contacts, items concerning other care givers and difficulties in knowing about the client's visits to private physicians).

10.5 Validation of the DRP-RAT in clinical practice (IV)

This study indicated that in most cases PNs were able to find those patients at high risk for clinically significant DRPs by using DRP-RAT. Thus, the Tool can be used in screening aged patients at risk for DRPs, and it provides clinically significant information for physician's decision making. The study also provided evidence on the highest priority risks that need action in geriatric pharmacotherapy.

10.5.1 ADRs as the highest priority risks for DRPs

This study brought some new information about the clinical importance of different risk factors for DRPs. The geriatrician reported that the most important patient information provided by the Tool was timely identification of symptoms suggestive of ADRs. She also classified the documented symptoms suggestive of ADRs as the most important risk factors for DRPs. The clinical importance of ADRs has been found also in several previous studies. Actually, ADRs have been recognized as the most common type of DRPs to result in severe harm jeopardizing patient safety (Pirmohamed et al. 2004, Patel et al. 2007, van der Hooft et al. 2008, Pedrós et al. 2016). However, in aged patients, the majority (40%–70%) of ADRs are judged to be preventable (Pirmohamed et al. 2004, Patel et al. 2007, van der Hooft et al. 2008) and thus, identification and early detection of ARDs are critically important (Davies and O'Mahony 2015). Involving more than one physician in patient's care, having more than one fall during the year prior the risk assessment, using high risk medicines, nonadherence and client's relative's/proxy's concern about the client's medicine use were also among the most important indicators of risk for DRPs.

Unlike several other studies, this study did not find the number of medicines or the number of daily doses to be among the most significant risk factors. Fulton and Allen reported that the risk of ADR is 13% when using two medications, increasing up to 58 % when using five medications (Fulton and Allen 2005). When using seven or more medications the incidence of ADRs increases to 82% (Prybus 2002). Several risk managing studies also list the number of medicines and/or number of daily doses as an important risk factor for DRPs (Koechler et al. 1989, Barenholz Levy 2003, Field et al. 2004, Fuller and Watson 2005, Johnson et al. 2005). One explanation for the differing result may be that the listed symptoms suggestive of ADRs are much stronger indicators as they measure the unwanted outcome of inappropriate prescribing or medicine use. It has also been stated that polypharmacy is not a problem if effectively managed. However, this cannot be considered as an explanation in this study as the patients had several DRPs. As a result of a strict validation process of the items included in DRP-RAT (I–III), all items are indicators for high risk of DRPs and thus, this study picked out the most significant risk predicting indicators which should be prioritized in medication risk management of the aged. The information about the most significant risk predicting indicators produced by this study may be useful when defining target groups for medication reviews. However, the finding about the risk predicting factors base on small population and thus, should be investigated more in detail with larger number of patients (Jirón et al. 2016).

10.6 Strengths and limitations of the study

10.6.1 Development and content validation of the DRP-RAT (I, II)

10.6.1.1 Literature searches (I)

Both literature searches conform to the PRISMA checklist (Moher et al. 2009). Together, the two literature searches cover risks related to the pharmacological effects of the medications but also risks related to the medicine use process and thus, enabled a comprehensive approach to risk management when developing the draft Tool. The unpublished literature search coved all relevant databases, such as Evidence Based Medicine Database, Web of Knowledge, Scopus and Cinahl which may be considered as a strength of this study. Restricting the first systematic search (I) to only two databases (MEDLINE and PubMed) may have limited the results of this study. We updated the first literature review in 2012, covering published studies until June 2012 (Dimitrow et al. 2013). Thus, our literature has a comprehensive coverage of potentially inappropriate medicines and medicine classes and is still quite well up-to-date, including, e.g., the update of the Beers criteria in 2012 (AGS 2012), but not the latest update in 2015 (AGS 2015). Also the EU(7)-PIM list is missing (Renom-Guiteras et al. 2015).

The search terms in both searches may have been insufficient. However, the searches were augmented with a manual search complementing the original search. As we only searched English language articles, criteria published in other languages were missed. Concerning the first literature search; most explicit criteria based on Beers criteria or their updates may have produced bias across the criteria, and thus, possible false conclusions and deficiencies may have remained throughout the criteria. This may introduce bias in the results of the first systematic review.

10.6.1.2 Delphi survey (II)

A Delphi survey's success depends on the selection criteria, process, and quality of the expert panel (Campbell and Cantrill 2001, Boulkedid et al. 2011, Diamond et al. 2014). To ensure a broad representation of skills and competence in geriatric care and pharmacotherapy, we invited panelists from three relevant but different expert professional groups: physicians, nurses, and pharmacists. Conducting the survey online facilitated broad geographic representation of that expertise. As the panelists were carefully selected from among the best experts in geriatric care and pharmacotherapy in Finland, we believe they had a comprehensive understanding for validating the content of the DRP-RAT. It may be considered a limitation that the expert panel did not include PNs although they were the designated end users of the DRP-RAT. The decision not to include PNs in the expert panel is justified as we wanted to have the best available expertise to validate the content of the tool. However, the structure of the draft DRP-RAT was developed taking in to account PNs' skills. Subsequently, PNs were strongly involved in the next steps (III, IV) of the validation process.

A multiprofessional 13–16-member expert panel responded in the three Delphi rounds. This is consistent with the panel size in several other Delphi surveys (Boulkedid et al. 2011). Thus, we believe that the number of participants is high enough to provide confidence in the stability of the

results. Response rates in the Delphi rounds in the current study varied from 76 to 94%, indicating the panelists' involvement and commitment to the development of the DRP-RAT. The strength of this study is also that we have reported response rates for all rounds, feedback was given between rounds, and we had the same criterion of consensus (80%) through all Delphi rounds which has not been self-evident in several other Delphi studies (Boulkedid et al. 2011).

Even though the draft DRP-RAT was initially based on two systematic literature reviews (I, Dimitrow et al. 2013, unpublished), the draft tool may have missed some relevant aspects of patient care. That is why the expert panelists were asked to suggest additional items based on their clinical expertise. We also drew on the research group's special expertise in geriatric pharmacotherapy and geriatrics to complement the evidence based origins for items in the final DRP-RAT. Thus, we believe that the development and validation processes have been rigorous enough to overcome potential deficiencies with the methodology.

10.6.2 Assessing the feasibility of the DRP-RAT among PNs and validation of the Tool in clinical practice (III, IV)

Triangulation was used in both studies when collecting the data. This research method consists of different types of approach (i.e., collecting both qualitative and quantitative data) and is the strength of this study, as it offers a wider approach in evaluating the validity of the DRP-RAT.

The small sample size in both studies (III; PNs n=36, IV; PNs n=26, patients n=46) may have limited the generalizability of the results. However, concerning study III, conducting the study in HC teams of two towns both having their own routines and practices in providing pharmacotherapy in PNs' normal working environment supports the validity of the results. Selection of PNs who participated in the training may have caused bias (participation was voluntary, not all PNs participated). It may also be a limitation that only one of the researchers made notes on the interactive discussions during both workshop days. This may have led the note-taker's individual views to impact on the notes.

The major limitations in study IV are a small sample size and the fact that the same geriatrician did all the medication reviews regardless of their comprehensiveness. When conducting the reviews using three different Medication Review Methods the geriatrician was instructed to be "blind" to her previous reviews for the same patient. How much the previous reviews finally affected on the next ones remains unknown. To reduce bias the order of the three medication review methods was carefully considered and the following order was applied: 1) based on DRP-RAT with medication list, 2) based on health centre's medical records and 3) based on methods 1 and 2 together.

According to the "gold standard" i.e., Medication Review Method 2, all patients were classified as "at-risk patients", which can be considered as a weakness of this study. Because of this result we were not able to compare "the at-risk patients" with "not at-risk patients" and the resolution power of the three Medication Review Methods used. To extrapolate the results of this study, future studies with larger number of patients and with more than one geriatrician are needed.

10.7 Future studies

The DRP-RAT is developed for PNs working in HC. However, it would be worth testing the Tool or parts of it i.e., the most important risk predicting factors, also in other settings, such as community pharmacies to identify risk patients but also to support medication reviews. In addition to community pharmacists, future studies may also engage clinical medication review pharmacists in medication risk management using the DRP-RAT. Also a patient or proxy administered version of the DRP-RAT would be worth developing and testing. A scoring system based on the importance of the items would help interpretation of the Tool. In Finland, we currently do not have clear target groups for medication review services (Chapter 4.2.1). The information about the most significant risk predicting indicators produced by this study may be useful when defining target groups for medication reviews. It would be worth testing to integrate the DRP-RAT in software programs to be used in mobile devices and as a part of a comprehensive geriatric assessment (CGA).

The PNs were delivered concrete applied pharmacotherapy education that could be implemented directly to their own work as well as to unit's medication management process. This kind of training related to pharmacotherapy risk management should be delivered more as continuing education. Future studies are needed to investigate the utility of integrating the training on the content and use of the DRP-RAT into PN curricula. Increasing knowledge about risks in geriatric pharmacotherapy sets a demand to update the DRP-RAT. Future studies are also needed to evaluate the effects of PNs' risk assessments using the DRP-RAT on clinical, humanistic and economic outcomes.

11 Conclusions

This PhD study indicates that the DRP-RAT, developed and validated in this study, could make it possible to more effectively involve PNs working in HC in medication risk management among home-dwelling aged, and that medication risk management should be focused on the highest priority risks. Unlike existing nurse-administered risk assessment tools focusing mainly on issues relating to adherence and medication management, the DRP-RAT focuses on the highest priority risks related to the pharmacological effects of the medications but also on factors related to the medication use process. Integrating a training to use the DRP-RAT into PN curricula is important. Future studies are needed to evaluate the implementation of the Tool in clinical practice and the effects of PNs' more systematic risk assessments using the DRP-RAT on clinical, humanistic and economic outcomes of geriatric pharmacotherapy.

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Appendix

The Drug-Related Problem Risk Assessment Tool (DRP-RAT) (II: Table 1)

1) Basic Client Data
Name
Identity number
Age: years
Gender: male female
Does the client live alone?
Does the client have an up-to-date medication card/list?
Who administers the client's medicines?
Is there anyone who determines whether the client takes his/her medicines?[a)]
2) Potential Risks for DRPs in Medication Use ("yes" or "no" answering options or select an appropriate item(s))
1. Does the client have seven[b)] or more prescription medicines in current regular use? (excluding basic creams)
2. Does the client take 12 or more medicine doses regularly each day (excluding basic creams)? Example of counting the doses: Drug 1: 1 tablet 3 times a day = 3 doses, Drug 2: 1 dose 2 times a day=2 doses, i.e., in total 5 doses a day
3. Is the client currently taking medicines for three or more diseases or symptoms? (including acute diseases)
4. Has the client started a new medicine in the last 4 weeks? (excluding different brands of the same active ingredient)
5. Does the client use medicines that; a) relieve pain by reducing inflammation (does not apply to paracetamol)? b) elevate the rate of urination (diuretics)?[b)] c) are intended to lower the cholesterol level (statins)[b)]? d) the physician does not know about?
6. Does the client use any of the following medicines (please check the ones used)? (the list contains medicines with a narrow therapeutic index, medicines for which regular monitoring would be necessary and medicines that otherwise are problematic for the aged) *amiodarone[b)], carbamazepine, digoxin, fluoxetine, lithium[b)], methotrexate[b)], theophylline[b)], warfarin*
7. Has the client used over-the-counter (OTC) medicines or vitamin, mineral or herbal products in the past two weeks? State which ones
8. Has the client had any of the following symptoms in the last 4 weeks? (Please tick below 'yes' if it has been ongoing and add another tick in the right column, if the symptom is a new one = a symptom that had first occurred within the last 4 weeks), *drowsiness, fatigue, skin rash or itch,*

dizziness, urination problems, muscle pains, nausea. diarrhea, constipation, dizziness when getting up, recurrent falls, swellings, memory problems, confusion, visual problems, stiffness, troubles in walking, low blood pressure; systolic pressure under 110 mmHg [b)]
9. Has the client had more than one fall in the past 12 months?
10. Has the client/relative/visitor noticed any changes in client's condition that could indicate adverse drug reactions related to changes in medicines regimen?
3) Characteristics of the Client's Care and Adherence ("yes" or "no" answering options or select an appropriate item(s))
a) Health, health care setting and care taking physician
11. Does the client have three or more chronic diseases?
12. Has the client been in short term care (e.g., interval care) in hospital, nursing home, sheltered housing, health centre ward or some other institution in the past 4 weeks?
13. Does the client have more than one physician involved in his/her care? (e.g., general practitioners, specialists, private practitioners)
b) Adherence
14. Has the client had troubles in; a) remembering to take the medicines? b) following the medicines regimen? c) knowing what his or her medicines are used for? d) affording the medicines (i.e., economic problems)? e) opening the drug bottles or packages or managing with medicines related therapeutic devices?
15. Does the client consciously sometimes take medicines differently than prescribed?
16. Is the client (or his/her caregiver) aware of the client's diseases and their treatments?
17. Is the client (or his/her caregiver administering the medication) aware of the medicines that the client uses?
18. Have the client's relatives/proxies expressed their concern about the client's medicine use?
4) Recommendations for Actions to Resolve DRPs (several items can be selected if necessary):
a) Comprehensive Medication Review, b) Using dose dispensing device, c) Automated dose dispensing [b)], d) Visiting the personal physician, e) Visiting a diabetes or asthma nurse in the health centre, or the diabetes or asthma pharmacist in the pharmacy [b)], f) Weekly control visits by a home care nurse, g) Follow-up of the client's condition (repeating the risk test) [b)]
Client's permission for possible intervening actions?
A short questionnaire about the client's alcohol consumption AUDIT C [a)] (Bush et al. 1998, Babor et al. 2001)
[a)] Included in DRP-RAT based on study III [b)]Retained in the DRP-RAT by judgement of the research group (II)

Original publications