Faculty of Pharmacy
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PROSPECTIVE MEDICATION RISK MANAGEMENT IN PRIMARY CARE:

ENHANCING COORDINATION OF CARE AND COMMUNITY PHARMACISTS' PARTICIPATION

Terhi Toivo

DOCTORAL DISSERTATION

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ABSTRACT

Over the last decade, a great deal of research has described the medication safety risks in hospitals and institutional care both in Finland as well as globally. Less attention has been paid to the safety of medicine use in outpatient care, even though majority of the use occurs at home.

The aim of this study was to enhance prospective medication risk management in outpatient care, by enhancing coordination of care with community pharmacists' participation and use of risk management screening tools available. Specific objectives of studies I–III were: I) to demonstrate how community pharmacies can utilize their prospective surveillance system for screening clinically significant drug-drug interactions (DDIs) in outpatients and assess the rate of DDIs in a large national prescription sample. II) To integrate risk assessment tools, procedures and databases available in Finland to form a coordinated medication management model (CoMM) for older home clients involving home care nurses and practical nurses (PNs), physicians and community pharmacists. III) To assess the impact of the CoMM on medication risks identified in drug regimens of older home care clients over a one-year period. Medication risks assessed related to potentially inappropriate medications (PIMs), excessive use of psychotropics, anticholinergic and serotonergic load, as well as clinically significant DDIs.

In study I, all DDI alerts issued by the online surveillance system were collected during a one-month period in 16 out of 17 University Pharmacy outlets in Finland, covering approximately 10% of the national outpatient prescription volume. The surveillance system was based on the FASS database, which categorizes DDIs into four classes (A–D) according to their clinical significance. Potential DDIs were analyzed for 276,891 dispensed prescriptions and they were associated with 11.2% of the prescriptions. Clinically significant DDIs categorized as FASS classes D (most severe, should be avoided) and C (clinically significant but controllable) were associated with 0.5% and 7.2% of the prescriptions, respectively.

Studies II–III were conducted in primary care in the city of Lohja, Southern Finland. Health care units involved were the home care, public primary healthcare center and a private community pharmacy. System-based risk management theory and the action research method were applied to construct the collaborative procedure utilizing each profession's existing resources in medication risk management of older ($\geq$65 years, n=191) home care clients.

Study II produced a 5-stage medication management model (CoMM) suitable for screening medications of a high number of home care clients and identifying clients with potential clinically significant drug-related problems (DRPs). The core of the model was the triage meetings that proved to be a feasible method for customizing comprehensiveness of collaborative medication reviews, according to their clinical needs while minimizing physicians' time demands.

In study III, an RCT study design was used to assess the impact of the CoMM on medication risks identified in drug regimens of older home care clients over a one-year period. Participants' (n=129) mean age was 82.8 years, 69.8% were female and mean number of prescription medicines in use was 13.1. The intervention did not show an impact on the medication risks between the original intervention group and the control group in the intention to treat analysis, but the per protocol analysis indicated a tendency for effectiveness, particularly in optimizing central nervous system medication use (benzodiazepines). Half (50.0%) of the participants with a potential need for medication changes, agreed on in the triage meeting, had none of the changes actually implemented.

Study I demonstrated that community pharmacists can actively contribute to DDI risk management and systematically use their surveillance systems for identifying patients with clinically significant DDIs.

In study II, the developed care coordination model (CoMM) was feasible for screening and reviewing medications of a high number of older home care clients in order to identify clients with severe DRPs and provide interventions to solve them, utilizing existing primary care resources. In study III, the CoMM intervention indicated a tendency for effectiveness when implemented as planned, particularly in optimizing CNS medication use during a 12-month follow-up.

Our study revealed that organizations and health care units involved in home care clients' medication therapy are currently working independently in silos, where no specific team membertakes holistic responsibility for medications. This study demonstrated the challenges to overcome when trying to change clinical practice and improve coordination between units involved in medication management of home care clients. Even though the outcomes of the intervention were not optimal, the value of the study is in discussing the real-world experiences and challenges of implementing new practices in home care.

This study indicated that practitioners in Finnish health care are not well acquainted with systems thinking, a fact which needs to be addressed in the future. Further studies are needed on care culture and other contributing factors to high prevalence of PIM use and other risks for clinically significant DRPs identified in this study. Particularly, further investigation is needed on system-based factors contributing to situations where identified preventable clinically significant medication risks are left unsolved, as well as the relationship between inappropriate medication use and medication errors.

A need for the organizational and national development of medication safety in primary care was identified in this thesis, which is line with the national and international publications, policy documents and recommendations. Furthermore, community pharmacists' contribution to medication safety, particularly in older adults, should be better utilized in the future, as this thesis shows promising demonstrations.

KEYWORDS
Medication risk management, medication-related risk, drug-drug interaction, primary care, home care, older adult, community pharmacy

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Toivo T, Mikkola J, Laine K, Airaksinen M. Identifying high risk medications causing potential drug-drug interactions in outpatients: a prescription database study based on an online surveillance system. *Res Social Adm Pharm* 2016; 12(4):559–68.

II Toivo T, Dimitrow M, Puustinen J, Savela E, Pelkonen K, Kiuru V, Suominen T, Uunimäki M, Kivelä SL, Leikola S, Airaksinen M. Coordinating resources for prospective medication risk management of older home care clients in primary care: procedure development and RCT study design for demonstrating its effectiveness. *BMC Geriatr* 2018; 18:74
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III Toivo T, Airaksinen M, Dimitrow M, Savela E, Pelkonen K, Kiuru V, Suominen T, Kinnunen S, Uunimaki M, Kivelä S-L, Leikola S, Puustinen J. Enhanced coordination of care to reduce medication risks in older home care clients in primary care: A randomized controlled trial. *BMC Geriatr* 2019; 19:332 doi: 10.1186/s12877-019-1353-2

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

DEFINITIONS OF THE KEY CONCEPTS

Adverse drug event (ADE)
Any injury occurring during the patient's drug therapy resulting either from appropriate care or from unsuitable or suboptimal care (Council of Europe 2006b). The definition includes adverse drug reactions (ADRs) and medication errors (MEs).

Adverse event (AE) (also terms patient safety incident and medical error are used)
An incident that results in harm to a patient (World Health Organization, WHO 2009). An adverse event is caused by medical management, in contrast to a process or complication of a disease (Council of Europe 2006a, 2006b).

Adverse drug reaction (ADR)
A response to a medicinal product that is noxious and unintended, resulting not only from the authorized use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorization, including the misuse, off-label use, and abuse of the medicinal product (EU Directive 2010/84EU1).

Clinical pharmacy
An area of pharmacy concerned with the science and practice of rational and appropriate medication use (American College of Clinical Pharmacy 2008; The European Society of Clinical Pharmacy (ESCP) 2017).

Community pharmacy
In Finland, community pharmacy is an authorized health care unit which is responsible for the supply and distribution of medicines to the public in outpatient care, as well as ensuring their safe and appropriate/rational use (Medicines Act 395/1987). In Finland, sale of medicines is limited to community pharmacies (excluding nicotine replacement therapy products). The obligations set for a community pharmacy vary in different countries.

Comprehensive medication review (CMR)
A collaborative medication review procedure implemented nationally in Finland, requiring accreditation training for pharmacists (Leikola 2012; AATE 2017; Kiiski et al. 2019). The procedure is based on collaboration between pharmacists and other healthcare professionals, particularly physicians. CMR includes 1) a patient interview and clinical medication review documented in a structured, evidence-based format and 2) a case report that documents recommended actions to manage clinically significant medication-related problems and a follow-up plan agreed upon in a collaborative case conference.

Coordination of care, care coordination
Care coordination, or coordination of care, is defined by the WHO as "a proactive approach to bringing together care professionals and providers to meet the needs of service users to ensure that they receive integrated, person-focused care across various settings" (WHO 2018).

Deprescribing
Deprescribing is an intervention intended to reduce harm associated with excessive polypharmacy. Deprescribing is defined as "the process of withdrawal of inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" (Reeve et al. 2015; Page et al. 2018).

Drug-related problem (DRP, also medication-related problem, MRP)
An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (Pharmaceutical Care Network, PCNE 2017).

Geriatric pharmacotherapy
Tailored pharmacotherapy for the older adults considering age-related changes in different organ systems and in the composition of the body, producing changes in pharmacokinetics (absorption, distribution, metabolism, and elimination) and pharmacodynamics of medicines. Furthermore, geriatric pharmacotherapy has a comprehensive approach to the medication therapy of older patients, considering multimorbidity, challenges with polypharmacy (e.g., drug-drug interactions, anticholinergic burden), potentially inappropriate medicines, as well as challenges in adherence and medicine use. Most often used age-limits for geriatric patients are: ≥65 years or ≥75 years (American Geriatrics Society 2019; Finnish Medicines Agency 2019).

Home care
Home care may be defined differently depending on the health care system in place. Most commonly, it is defined as patients living at home with the support of professional caregivers (mostly nursing professionals), employed by a professional home care organization (Meyer-Massetti et al. 2018). In Finland, municipal home care services are a part of the public health care system, encompassing social and health services including home help and home nursing (Keskimäki et al. 2019).

Medication error (ME)
Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer (National Coordinating Council of

Medication Errors Reporting 1998). Such events may be related to professional practice, healthcare products, procedures and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication safety
A 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 medications (Council of Europe 2006a and 2006b; World Health Organization 2009).

Medicines optimization
Medicines optimization is defined as "a person-centered approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines" (National Institute for Health and Care Excellence 2015).

Multimorbidity
Multimorbidity is defined as the presence of two or more chronic health conditions, which can include (a) defined physical and mental health conditions; (b) ongoing conditions such as learning disability; (c) symptom complexes such as frailty or chronic pain; (d) sensory impairment such as sight or hearing loss; and (e) alcohol and substance misuse (National Institute for Health and Care Excellence 2016; WHO 2019).

Older adults (or older persons, elderly)
Most developed countries have accepted the chronological age of 65 years as an age limit of 'elderly' or older persons (WHO 2010). The thesis applies this definition.

Patient safety
Freedom from accidental injury during the course of medical care; activities to avoid, prevent or correct adverse outcomes which may result from the delivery of healthcare (Kohn et al. 2000; Council of Europe 2006b; WHO 2009).

Pharmaceutical care
The core of pharmaceutical care is medication risk management by identifying, solving and preventing medication-related problems. According to the principles of pharmaceutical care, the role of pharmacists in patient care is to ensure the quality of medication therapies, with an emphasis on interprofessional collaborative care and patient interaction (Hepler & Strand 1990; American Society of Hospital Pharmacists 1993; Cipolle 2004; American College of Clinical Pharmacy 2008; Pharmaceutical Care Network Europe 2013).

Polypharmacy
Polypharmacy refers to the concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications (Masnoon et al. 2017; WHO 2019). This includes prescription medicines, over-the-counter and/or traditional and complementary medicines used by a patient. Excessive polypharmacy is defined as the concomitant use of nine/ten or more medicines taken regularly or as-needed (Onder et al. 2012). Polypharmacy can be appropriate or inappropriate (Scottish Government Polypharmacy Model of Care Group 2018).

Potentially inappropriate medication/medicine (PIM)
Medication that may be inappropriate for older individuals. It can be considered as inappropriate because of questionable effectiveness, unfavorable benefit-risk ratio or because safer alternatives exist (Beers et al. 1991; Dimitrow et al. 2011; American Geriatrics Society 2019).

Primary care (PC)
Primary care is a key process in the health system (WHO 2020). Primary care typically acts as the first contact and principal point of continuing care for patients within a healthcare system, and coordinates other specialist care that the patient may need. First-contact care is accessible at the time of need; ongoing care focuses on the long-term health of a person rather than the short duration of the disease; comprehensive care is a range of services appropriate to the common problems in the respective population and coordination is the role by which primary care acts to coordinate other specialists that the patient may need. PC is a subset of primary health care (PHC) (WHO 2020).

Primary health care (PHC)
Primary health care refers to the concept elaborated in the 1978 Declaration of Alma-Ata, which is based on the principles of equity, participation, inter-sectoral action, appropriate technology and a central role played by the health system (WHO 2020).

Risk management, prospective risk management
Activities or measures taken by an individual or a healthcare organization to prevent, remedy or mitigate the occurrence or reoccurrence of a real or potential (patient) safety event (Dückers et al. 2009).

Safety culture
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).

Systems approach

An approach to safety stating that errors are generally consequences of systemic factors, e.g., weaknesses in organizational structures and processes (Reason 2000). Building systemic defenses to reduce and prevent errors is the main method of safety improvement in a systems approach.

Triage meeting
In this study, triage meeting refers to the method used for customizing comprehensiveness of collaborative medication reviews for older home care clients according to their clinical needs while minimizing physicians' time demands.

ABBREVIATIONS

AATE	The National Coordination Group of Professional Development of Pharmacy Services in Finland
ADD	Automated dose dispensing
ADE	Adverse drug event
ADR	Adverse drug reaction
AFP	The Association of Finnish Pharmacies
AGS	American Geriatric Society
ASHP	American Society of Health-System Pharmacists
ATC	Anatomical Therapeutic Chemical
CDSS	Clinical decision support system
CGA	Comprehensive Geriatric Assessment
COMET	The Core Outcome Measures for Effectiveness Trials
CoE	Council of Europe
CMR	Comprehensive medication review (Finland)
DDI	Drug-drug interaction
DRP	Drug-related problem
DRP-RAT	Drug-Related Problem Risk Assessment Tool
DUR	Drug Utilization Review (United States)
EU	European Union
ESCP	European Society of Clinical Pharmacy
EUNetPaS	European Union Network for Patient Safety
Fimea	Finnish Medicines Agency
HaiPro	Reporting System for Safety Incidents in Health Care Organizations (Finland)
ISMP	Institute for Safe Medication Practices (United States)
JCAHO	Joint Commission Accreditation of Healthcare Organizations (United States)
ME	Medication error
MSAH	Ministry of Social Affairs and Health (Finland)
MTM	Medication Therapy Management
NCC MERP	National Coordinating Council of Medication Errors Reporting (United States)
NHS	National Health Service (United Kingdom)
NICE	National Institute for Health and Care Excellence (United Kingdom)
OTC	Over-the-counter
PCNE	Pharmaceutical Care Network Europe
PN	Practical nurse
PIM	Potentially inappropriate medicines
RCT	Randomized controlled trial
SII	Social Insurance Institution of Finland

THL	National Institute for Health and Welfare (Finland)
WHO	World Health Organization

1 INTRODUCTION

Pharmacotherapies have evolved remarkably during the last few decades. Better therapeutic outcomes are being achieved and a growing number of medical conditions can be managed by modern pharmacotherapies. For many diseases, pharmacotherapy has become the primary form of treatment alongside lifestyle changes.

At the same time as therapeutic outcomes have improved, medication loads of individuals have grown. Polypharmacy has become more prevalent, creating new challenges for healthcare providers in the design, implementation and monitoring of medication therapies on a patient-by-patient basis (WHO 2019). This is particularly the case with pharmacotherapy of older adults. In Finland, for example, a high proportion of the medication load is concentrated on a small population segment aged ≥65 years and with multimorbidity (Saastamoinen & Verho 2015).

If medication therapies are not properly implemented, the intended benefits may not be achieved and the risks may outweigh the benefits. This can lead to preventable harm and human suffering, as well as preventable direct and indirect costs caused by medicines. There is growing evidence that medicines are a major cause of errors in patient care, and many of these errors occur in older patients (WHO 2017a, 2019).

Over the last decade, a great deal of research has described the risk situations and errors caused by medicines in hospitals and institutional care both in Finland and globally (Kohn et al. 2000; Holmström 2017; Schepel 2018; Schepel et al. 2018; Schepel et al. 2019). Patient and medication safety work and monitoring of safety risks have been focused on institutional care. Less attention has been paid to the safety of medicine use at home, even though a majority of the use occurs at home (Panesar et al. 2016).

The origins of this study date back 20 years, when a national program (TIPPA) was initiated in Finland in order to develop medication counseling in community pharmacies to promote rational and safe use of medicines (TIPPA Project 2004; Puumalainen 2005; Kansanaho 2006). The primary goal was to support each pharmacy to establish a long-term development plan for improving their counseling services. The four-year program was funded by the Ministry of Social Affairs and Health, the Social Insurance Institution of Finland (Kela), the Finnish Medicines Agency and the key stakeholders in community pharmacy sector.

During the TIPPA project, it became evident that there were many problems and risks inherent in the medication therapies of outpatients that could not be solved by counseling the patients in the pharmacy: a need for a more comprehensive assessment of medication therapy in collaboration with the patient and professionals involved in their care was identified. This initiated a long, ongoing journey towards implementation of collaborative

medication reviews in Finland, which have evolved into various practices for different healthcare settings (Leikola 2012; Kiiski et al. 2019).

The aim of this study was to find solutions for prospective risk management and quality improvement of pharmacotherapy of older adults that could be transferred to other similar local healthcare settings. This demonstration study, conducted in home care of city of Lohja in Southern Finland in 2015–2018 and funded by the Social Insurance Institution of Finland (Kela), focused on enhancing coordination between home care and community pharmacy by developing a prospective medication risk management procedure for older home care clients. The aim was to make better use of the existing scarce resources, including home care, health center and pharmacy staff, home care clients and their family members, databases and tools available in community pharmacy to assist with medication risk management.

The literature review of this doctoral thesis provides a basis for understanding the systems approach and prospective risk management of medication therapies and its implementation in primary care, especially in home care and community pharmacies. A special emphasis was placed on clinically significant drug-drug interactions as they were the first medication-related risks that have been systematically screened with the help of electronic tools both in Finland and elsewhere.

2 REVIEW OF THE LITERATURE

2.1 PRINCIPLES OF PROSPECTIVE MEDICATION RISK MANAGEMENT

Although patient safety, i.e., the principle of not harming patients, has always been a priority in patient care, it received more visibility and concrete content in the early 2000s, when the principles of systems-based patient safety were introduced. The global systems-based patient safety movement was initiated by the US Institute of Medicine's landmark report "To Err Is Human: Building a Safer Health System" which was launched in 2000 (Kohn et al. 2000).

Since medications have shown to contribute to a high number of risk situations and actual medication errors, medication safety has been a central part of systems-based patient safety work from the outset (Kohn et al. 2000; Council of Europe 2006b; Institute of Medicine 2007; WHO 2009, 2017a). This chapter briefly describes the theoretical framework, key concepts and the shift in focus towards prospective risk management in the systems-based patient and medication safety work.

2.1.1 THEORETICAL FRAMEWORK FOR SYSTEMS-BASED RISK MANAGEMENT IN HEALTH CARE

The simplest definition of patient safety is the prevention of errors and adverse effects to patients associated with health care (WHO 2009). Patient safety consists of the identification, analysis and management of patient-related risks and incidents, in order to make patient care safer and minimize harm to patients (WHO 2017b).

In health care, risk management is defined as "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 2006b). Prospective medication risk management focuses on developing strategies for 1) identifying and managing medication risks before harm occurs or 2) minimizing actual harm.

One of the most widely used theories to explain safety risks and their management is psychologist James Reason's Human Error theory (Reason 2000). It has been facilitating the shift in risk management thinking from an individual to systems level (Reason 2000). Human Error theory introduced two approaches to the challenge of human error. The person's approach which has been dominant in health care focuses on individuals as a cause of error. The individuals can be blamed for being forgetful, inattentive or incompetent, leading to harmful consequences. The systems approach focuses on the conditions under which people work and tries to build systemic defenses to prevent errors from occurring or minimizing their harmful effects.

Reason's (2000) systems approach is often illustrated by the Swiss Cheese Model which visualizes the idea of managing the risks of organizational accidents (Figure 1). Concerning risk management in health care, the Swiss Cheese Model helps to evaluate health care processes and to identify potential safety risks. The same applies to systems and processes in medication therapy management: they need to be developed so that risks are identified, and appropriate systemic defenses are implemented in the process.

The global systems-based patient safety work was initiated by the US Institute of Medicine's (IOM) landmark report "To Err Is Human: Building a Safer Health System" (Kohn et al. 2000). The report highlighted the systems approach introduced by the Theory of Human Error (Reason 1990, Reason 2000), and stated that the problem was not incompetent people in health care – it is that good people are working in bad systems which need to be made safer (Kohn et al. 2000). Wide-ranging recommendations were presented for improving patient safety, in the areas of leadership, improved data collection, and analysis, and development of effective systems at the level of direct patient care.

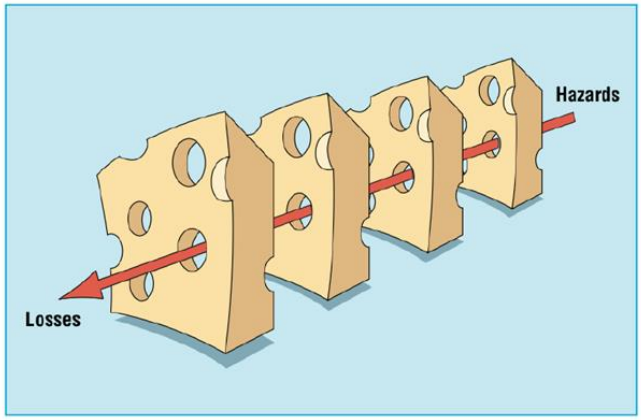


Figure 1 The Swiss Cheese Model illustrating system accidents (Reason 2000)

2.1.2 COORDINATION OF PATIENT AND MEDICATION SAFETY WORK AT GLOBAL, EUROPEAN AND NATIONAL LEVEL

Following the IOM report (Kohn et al. 2000), the Council of Europe (CoE) established expert groups to evaluate the situation in Europe and to provide recommendations for improving patient and medication safety at the European level (Council of Europe 2006a, 2006b). The CoE stated that medication errors were poorly managed in Europe and suggested that European healthcare organizations start to work in the following areas to improve medication safety (Council of Europe 2006a, 2006b):

- Establish and use a common terminology concerning harm to patients caused by medication and promote a common taxonomy to facilitate the sharing of safety information in Europe;
- Create a culture of safety and best practices;
- Develop medication error reporting systems for both hospitals and primary care; and
- Set up a national focal point for safe medication practices.

Since then, various initiatives have been implemented in Europe to promote patient and medication safety. In 2008, the European Union (EU) launched the EUNeTPaS (European Union Network for Patient Safety) project to promote patient safety culture (European Union Network for Patient Safety 2008). This was followed by the European Union Network for Patient Safety and Quality of Care (PaSQ) Joint Action, which was co-founded and supported by the European Commission, in order to support the implementation of the EU Council Recommendation on Patient Safety (The European Union Network for Patient Safety and Quality of Care 2012). Concerning medication safety, the PaSQ program mainly focused on establishing and improving medication reconciliation practices.

At a global level, the WHO has taken a facilitating role in patient safety development, for instance with global patient safety challenges (WHO 2017a). The Global Patient Safety Challenges identify a patient safety burden that poses a significant risk to health, and then develop frontline interventions and partner with countries to disseminate and implement the interventions (WHO 2017a). The first Global Patient Safety Challenge aimed to reduce healthcare infections through improved hand hygiene (Clean Care is Safer Care in 2004). The second one concerned risks associated with surgery (Safe Surgery Saves Lives in 2008). The third Global Patient Safety Challenge, released in 2017, focuses on medication safety (WHO 2017a). The goal of the "Medication without Harm" program is to reduce the level of severe avoidable harm related to medication by 50% over 5 years, globally. The Challenge focuses on improving medication safety by strengthening the systems for reducing medication errors and avoidable medication-related harm. The key areas of the challenge are high-risk situations, polypharmacy, and transitions of care. High-risk situations include high-risk settings, e.g., hospital settings with more serious clinical situations and the use of more complex medications, high-risk patients, e.g., young children, older adults, patients with concomitant kidney or liver disease and high-alert medications associated with a high risk of severe harm if used improperly.

2.1.2.1 National level

Global patient and medication safety trends and their launch in Europe worked as a driving force for the initiation of the work undertaken in Finland in the early 2000s (Airaksinen et al. 2012; Holmström 2017; Schepel 2018).

The early phase medication safety work in Finland focused on adopting the prospective risk management approach through "Swiss Cheese thinking". This may be due to the fact that Finland was an active member in the Council of Europe's (CoE) expert groups on patient and medication safety in 2003–2006 (Council of Europe 2006a, 2006b; Airaksinen et al. 2012). The CoE recommendations on medication safety inspired the National Centre for Pharmacotherapy Development (Rohto) to establish a multidisciplinary working group on medication safety in 2004. The working group developed a Finnish glossary of terms related to patient and medication safety using a systems approach (Stakes & Rohto 2006; Toivo & Airaksinen 2006). The glossary was based on the glossary published as part of the CoE medication safety report (Council of Europe 2006b) and it is still widely used.

Another remarkable step in the early phase of systems-based medication safety work in Finland was the development of a guide of safe medication practices in health care organizations (Ministry of Social Affairs and Health 2006). The core of the guide was instructions to create a unit-based medication safety plan which describes in-house safe medication practices. The plan was recommended to include a description of the medication use processes and medications in use in the unit, as well as competences, responsibilities, and tasks of the staff regarding safe medication management. The Safe Pharmacotherapy Guide emphasized learning from MEs through a systems approach (Ministry of Social Affairs and Health 2006; Airaksinen et al. 2012). The Guide was updated in 2015 and the third version is currently underway (Finnish Institute for Health and Welfare 2015). The organization-based medication safety plans became obligatory in 2011, as part of patient safety plans (Health Care Act 1326/2010). Establishment of the medication safety plans has been supported by, e.g., audit tools that assist in identifying areas in medication management processes that need improvement (Teinilä et al. 2012; Celikkayalar et al. 2016; Suvikas-Peltonen et al. 2016).

Crucial for the successful implementation of medication safety initiatives in Finland has been the fact that the medication safety work has been closely integrated into patient safety work since the beginning. The establishment of the National Patient Safety Network (2005) and the Patient Safety Steering Group (2006) by the Ministry of Social Affairs and Health were important first steps in this respect (Ministry of Social Affairs and Health 2009b; Airaksinen et al. 2012; Holmström 2017). The Patient Safety Network comprised of approximately 200 members representing healthcare professionals and providers, patients, non-governmental organizations, authorities, researchers, and educators.

The mandate of the MSAH Patient Safety Steering Group 2006–2009 was to promote patient safety and to coordinate initiatives at national level. The key targets of the Steering Group were to establish the first national patient safety strategy and guidelines for reporting adverse events in health care (Holmström 2017). In its final report, the Steering Group emphasized the importance of a prospective approach in promoting patient safety (MSAH,

2009b). An important action was the launch of the reporting system of adverse events (HaiPro) in 2007, for the purpose of learning from errors and near misses. HaiPro is still widely in use in health care organizations and has provided valuable information on safety risks in Finnish health care (Härkänen 2014; Holmström 2017; Laatikainen 2020). As it also includes information on medication errors, it has helped to understand the magnitude of medication safety risks as part of all adverse events (Ruuhilehto et al. 2011; Härkänen 2014; Holmström 2017; Laatikainen 2020). Learning from retrospectively reported safety incidents has laid the foundation for prospective medication risk management actions (i.e., systemic defenses), particularly in hospitals. A good example of the earliest actions in this respect is establishing guidelines for safe use of high-risk medications (Tyynismaa et al. 2017; Schepel et al. 2018) . The challenge is that HaiPro is still primarily in use in inpatient care units: safety data is missing from outpatient care despite that most of the medicines are used in this context.

A major effort of the Patient Safety Steering Group was the development of the first National Patient Safety Strategy (covering 2009–2013) (Ministry of Social Affairs and Health 2009). The goal was to use the Strategy as a vehicle for integrating patient safety into the existing healthcare structures. The integration was enacted in 2011 through the new Health Care Act (1326/2010, §8).

The Finnish Society for Patient Safety was founded in 2010 to implement patient safety initiatives (Holmström et al. 2015b). The society has a special section on medication safety.

Most recently, many of the challenges in managing medication risks have been addressed in the Rational Pharmacotherapy Action Plan 2018–2022, established in 2018, as well as in its implementation program (roadmap) by 2030 (Ministry of Social Affairs and Health 2018, 2019).

Community pharmacies have been actively involved in medication safety work. Pharmacies ran a national Medication Safety Program (APILA 2012–2015) as part of nationally coordinated Patient Safety Program aimed to implement the first patient safety strategy (THL 2011–2014) (Airaksinen et al. 2012). The goals of the APILA Program were two-fold (Airaksinen et al. 2012; Kuitunen et al. 2014). First, the goal was to promote medication safety within community pharmacies by improving their internal systems and processes. The second goal was to contribute to medication management systems and processes in primary care to improve medication safety.

2.1.3 KEY CONCEPTS OF MEDICATION SAFETY

The Council of Europe's working group on medication safety conducted an extensive inventory of concepts related to the systems approach to patient and medication safety (Council of Europe 2006b). The Council of Europe glossary was recommended to be translated into national languages for creating

awareness and establishing shared understanding of key patient safety concepts among healthcare providers. A condensed version was published in Finland in 2006 (Stakes & Rohto 2006; Toivo & Airaksinen 2006).

The Finnish glossary illustrated the core elements of patient safety as presented in Figure 2 (Stakes & Rohto 2006; Toivo & Airaksinen 2006). Safety of pharmacotherapy was divided into product safety (i.e., drug safety) and process safety (i.e., medication safety). The term 'drug safety' was recommended to be used when evaluating adverse events during clinical trials, and when evaluating adverse drug reactions (ADRs) of correctly prescribed, dispensed and administered drugs (Council of Europe 2006b). Thus, the concept of drug safety relates to the safety of pharmaceutical products, focusing on adverse drug reactions (ADRs) which are studied with pre- and postmarketing activities in pharmacovigilance.

On the other hand, medication safety (i.e., process safety) refers to managing medication errors (MEs) which are defined as unintended mistakes in the medication use process caused by omission (a mistake caused by not doing something that should have been done) or commission (a mistake caused by doing something wrong) (Figure 2), (Council of Europe 2006b; Stakes & Rohto 2006; Toivo & Airaksinen 2006). The CoE used the US definition of medication errors, which has been widely used internationally since its launch in 1998 (National Coordinating Council of Medication Errors Reporting and Prevention 1998). According to the definition, an ME is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Medication errors may occur during any stage of the medication use process, e.g., when prescribing, dispensing or administering a medicine. Such events may relate to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use". A near miss (called also a close call or a potential adverse drug event), is an incident that has the potential to cause a serious medication error or adverse drug event, yet did not, either by chance or through timely preventive intervention (Figure 2) (Council of Europe 2006b). An adverse drug event (ADE) is defined as "any injury occurring during the patient's drug therapy resulting from either appropriate care, or from unsuitable or suboptimal care" (Council of Europe 2006b). The definition of ADE includes ADRs and MEs.

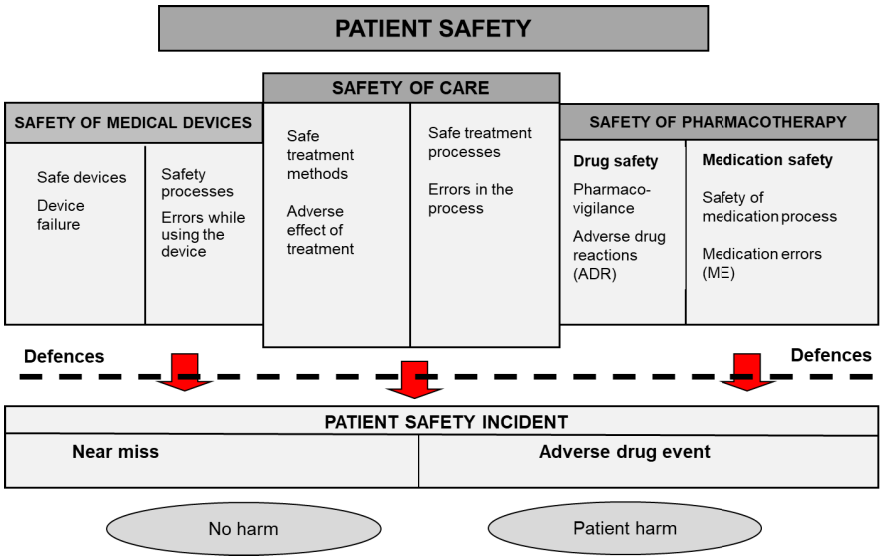


Figure 2 Terms related to patient safety and medication safety as part of it (adapted from Stakes & Rohto 2006)

Figure 2 remains valid for outlining patient and medication safety concepts, even though it was created in 2006. However, there has been, for example, integration of ME and ADR concepts in EU pharmacovigilance legislation since then. The current pharmacovigilance legislation was approved in 2010 and it came into effect in July 2012 (Directive 2010/84/EC and Regulation (EC) 1235/2012). The legislation introduced significant changes in ADR management (Santoro et al. 2017; Inácio 2018). One of the biggest changes relates to the widening of the legal definition of an ADR. An ADR is currently defined as a response to a medicinal product which is noxious and unintended, arising from the use of the medicinal product within or outside of marketing authorization, or from occupational exposure. The use outside of marketing authorization covers off-label use, overdose, misuse, abuse, and medication errors (European Medicines Agency 2017).

2.1.4 PROSPECTIVE MEDICATION RISK MANAGEMENT

Retrospective medication error reporting and analyzing medication error reports for learning purposes have been fundamental for understanding medication use processes and related patient safety risks in various health care settings (Kohn et al. 2000; Härkänen 2014; Council of Europe 2006a and b; Holmström 2017; Schepel 2018; Laatikainen 2020). Learning from medication errors and near misses has led to the restructuring of medication use processes and building up of new systemic defenses or strengthening existing ones in order to prevent risks and errors (Figure 2). Thus, an increasing shift towards prospective risk management can be seen in patient

and medication safety initiatives, although retrospective error reporting is still needed and recommended as part of risk management (e.g., WHO 2017). Various prospective risk management tools, including drug-drug interaction screening tools, criteria for potentially inappropriate medicines for older adults and various decision support systems, have been developed and widely implemented.

The WHO's Medication Without Harm program is a good demonstration of the current prospective risk management shift and its priority areas (WHO 2017). The program has prioritized major risks and the best evidenced actions for their prevention. The risks seem to be universal, regardless of the health system.

One of the core risk areas prioritized by the WHO is geriatric pharmacotherapy (WHO 2017). The evolution of prospective risk management methods and tools has been fast, especially over the last few decades, with increasing evidence of medication safety risks in this growing population segment (Airaksinen et al. 2012; Holmström 2012; Dimitrow 2016). Among the useful tools to prevent medication risks have been explicit and implicit criteria to decrease prescribing of potentially inappropriate medicines (PIMs) for older adults (Beers et al. 1991; Spinewine et al. 2007b; Dimitrow et al. 2011; Lucchetti & Lucchetti 2017; American Geriatrics Society 2019). In order to be effective, these criteria need to be implemented in routine clinical practice throughout health care. Recently, the implementation has been facilitated through electronic medication risk management databases, software applications and clinical decision support systems (CDSS), which have dramatically evolved over the last decade (Schiff et al. 2016). The databases and CDSS systems can prospectively detect PIMs and other medication safety risks, though qualified health care professionals are needed to make the final decision using clinical judgement based on comprehensive patient information.

Finland is one of the countries with advanced national health portals, databases and prospective screening systems for managing medication-related risks (Heikkilä et al. 2006; Dimitrow et al. 2014; Duodecim 2019). Within less than 20 years, a wide range of medication risk management tools have been developed, with the Finnish Medical Society Duodecim playing a major role in their development (Duodecim 2019). These tools are widely available in Finnish health care, including community pharmacies. Efficient use of these modern tools and skill-sets requires coordinated medication management processes in different healthcare settings. However, this is not the case in many countries, including Finland (Kallio et al. 2016).

2.2 PATIENT AND MEDICATION SAFETY IN PRIMARY CARE

Globally, primary care forms the foundation of any health system, and the majority of people in need of medical care are managed in primary care units (WHO 2012; Panesar et al. 2016; WHO 2016a). Therefore, the quality and safety of care in primary care is a major health policy and public health issue. However, patient and medication safety initiatives and research have mainly focused on hospital care (WHO 2016a), although understanding the magnitude and nature of safety risks in primary care has a growing importance.

This chapter briefly discusses the structure and function of primary care in Finland, and its operation in relation to specialized care. Thereafter, patient and medication safety in primary care will be addressed in a global context in the light of the challenges raised by the WHO.

2.2.1 PRIMARY CARE IN THE FINNISH HEALTH SYSTEM AND SAFETY CHALLENGES

In Finland, the health care system is based on a public system, which is complemented by private and occupational healthcare services. The services are divided into primary care and specialized care services. Municipalities are responsible for organizing primary healthcare services, which are mainly provided by municipal health centers (Health Care Act 2011). Secondary special healthcare is organized by central hospitals, each of them located in their own hospital districts (n=21) owned by federations of municipalities (Keskimäki et al. 2019). For special tertiary healthcare, Finland is divided into five areas of responsibility (Helsinki, Turku, Tampere, Kuopio and Oulu), each with a university hospital. Primary care carries the main responsibility of care, and all patients admitted to secondary or tertiary care need a referral from primary care. The care is coordinated by the patient's primary care physician.

Municipalities (i.e., local authorities) are responsible for organizing and financing primary and specialized care in the public healthcare system. The system is funded by multiple funding sources: municipalities, government, employers, and through taxation of residents as well as service fees for services users (Keskimäki et al. 2019; Ministry of Social Affairs and Health 2020). Funding channels are separate for primary and specialized health care. Legislation and general policy guidelines are prepared at the national level, with municipalities and hospital districts having a large degree of freedom in the organization of services. Three main acts, the Primary Health Care Act (1972), the Act on Specialized Medical Care (1991) and the Health Care Act (2010), set the framework for regulation and governance of health services in Finland (Keskimäki et al. 2019).

All residents are equally entitled to public, municipal primary care. Primary care is provided by health centers, which provide primary curative, preventive

and public health services to its population. Typically, health centers provide the following services: 1) ambulatory curative care, both for acute and chronic patients; 2) preventive services, including maternity and child clinics; 3) home nursing for older people or for selected groups of chronic patients; 4) dental health services; 5) rehabilitation in various forms; and 6) mental health services and substance abuse services (Hetemaa 2018). The most typical patients of health centers are the very young and elderly, and those of lower socioeconomic or educational levels (Kestilä & Karvonen 2019). This is due to the co-existing occupational and private health care systems.

Pharmacotherapy for primary care outpatients is dispensed from private community pharmacies and from university pharmacies owned by the University of Helsinki and the University of Eastern Finland (altogether 815 pharmacy outlets in 2018). The community pharmacy system is highly regulated to ensure its commitment to the national health policy goals (Ministry of Social Affairs and Health 2018). By law, community pharmacies' main functions are to ensure an adequate supply of prescription and nonprescription medicines, and their safe, appropriate and economical use for the general public (Medicines Act 395/1987).

In pharmacotherapy, the key challenges in primary care relate to the lack of coordination of care, as identified in the National Medicines Agency's program to optimize medicine use among older adults (Kallio et al. 2016; Kumpusalo-Vauhkonen et al. 2016). Information on individual patient's medications and diagnoses is scattered and may vary at different levels of the public health service, and information does not transfer between health care providers involved in care team (Kallio et al. 2016).

Even though the importance of an accurate and up to date medication list is acknowledged, many patients do not yet have it (Sinnemaki et al. 2014; Kekäle 2016; Schepel et al. 2019).

With long-term medications, major development needs identified in medication use process relate to poor access to patient information and its transfer in healthcare, particularly the lack of reconciled medication lists and electronic health records; poorly functioning medication use process in home care and social care units; and limited patient involvement in their care (Mononen et al. 2020). Furthermore, the system-based factors have found to lead to a situation where no one truly takes comprehensive responsibility for patients' medications, leading to medication safety risks (Kallio et al. 2016, Kumpusalo-Vauhkonen et al. 2016, Mononen et al. 2020).

These identified challenges are considered in the ongoing Rational Pharmacotherapy Action Plan 2018–2022 by the Ministry of Social Affairs and Health (Ministry of Social Affairs and Health 2018).

2.2.2 PATIENT SAFETY RISKS IN PRIMARY CARE – A GLOBAL VIEW

Every day, millions of people across the world use primary care services, as they provide an entry point into the health system (WHO 2016a). Good quality

and accessible primary care may lead to fewer avoidable hospitalizations, while unsafe primary care can cause avoidable illness and harm, leading to unnecessary hospitalizations and in some cases, disability, and even death (WHO 2016a). Therefore, the potential and necessity to reduce primary care-related harm is considerable.

To date, however, most patient safety research has focused on hospital settings, and not on primary care where majority of health care is actually delivered (WHO 2016a, WHO 2017). There are differences in the type of clinical problems faced, the role of the patient, classes of medications used and the organization of services in primary care compared to hospital settings. This means that the risks posed in primary care and the solutions required may differ from those in hospital settings.

The global shift towards primary care-based care structures has been supported by the WHO in low-income and middle-income countries and by economic pressures in industrialized nations (WHO 2012). Therefore, it has become essential to advance the understanding and awareness of the risks to patients in primary care, the magnitude and nature of preventable harm due to unsafe practices, and effective mechanisms to protect patients. Recognizing the limited information available on primary care, the WHO set up a Safer Primary Care Expert Working Group in 2012 (WHO 2012). The Working Group reviewed the literature, prioritized areas needing further research, and published essential next steps (WHO 2012). Following this, much work has begun, e.g., with increasing research evidence and providing guidance for key safety risks in primary care (Panesar et al. 2016, WHO 2016a). The WHO developed a Technical Series on Safer Primary Care with technical reports providing practical guidance of identified key safety risks and their management. The Series consists of nine monographs related to patients (WHO 2016b), health workforce (WHO 2016c, 2016d), care processes (WHO 2016e, 2016f, 2016g, 2016h, 2016i) and tools and technology (WHO 2016j). The reports explore the magnitude and nature of harm and provide some potential solutions for improving safety in primary care. The topics covered in the series are:

- Patient engagement (WHO 2016b)
- Education and training (WHO 2016c)
- Human factors (WHO 2016d)
- Administrative errors (WHO 2016e)
- Diagnostic errors (WHO 2016f)
- Medication errors (WHO 2016g)
- Multimorbidity (WHO 2016h)
- Transitions of care (WHO 2016i)
- Electronic tools (WHO 2016j).

These topics cover a wide range of system-based factors, as well as patient-related factors contributing to safety in primary care. Patient engagement was identified as a key area when aiming to reduce medication-related problems.

The Patient Engagement report highlights educating patients and health care providers and encouraging people to ask questions or speak about their concerns (WHO 2016b). The Education and Training report focuses on competences of primary care providers, highlighting shortcomings in education requiring action related to medication safety (WHO 2016c). The Human Factors report addresses the safety problem and highlights systems-based thinking in risk management and the importance of building systemic defenses so that errors are less likely to result in harm (WHO 2016d). The Medication Errors report brings up injection use, pediatrics, and care homes as key areas requiring special consideration (WHO 2016g). Multimorbidity report highlights the need for systems approach in the care of people with multiple conditions and polypharmacy (WHO 2016h). Enhanced communication and coordination across different health care system levels is needed, as well as self-management support. People with multiple conditions may need specialist care with some health issues, but their overall health care needs are likely to be best met by medical generalists.

The WHO primary care document highlights that understanding the epidemiology of errors in the primary care context is crucial to understanding risk factors and developing strategies to reduce the risk of iatrogenic harm (WHO 2012). Thus, the WHO commissioned an extensive systematic review to investigate patient safety incidents in primary care and the resulting severe harm (Panesar et al. 2016). A systematic literature review, with 18 databases, was conducted on studies published between January 1980 and July 2014. The number of screened articles was 61,521, of which nine systematic reviews and 100 primary studies were included. Of the studies, 36% were from the USA or Canada, 39% from Europe, 13% from other OECD countries and 12% from non-OECD countries.

The systematic review by Panesar et al. (2016) suggested that patient safety incidents are relatively frequent in primary care, though most of them do no result in severe harm to patients. Studies reported between < 1 and 24 patient safety incidents per 100 consultations. Due to the heterogeneity of studies, it was not possible to provide a single value of the frequency of incidents, but a median of around 2–3 incidents per 100 consultations/patient records was suggested.

Based on studies that had documented the type of safety incidents, the following three most common safety incident categories were identified: 1) administrative and communication incidents; 2) diagnostic incidents; and 3) prescribing and medication management incidents (Table 1). Studies based on retrospective patient record reviews had a median estimate of 4% of all documented incidents being associated with severe harm, defined as significantly impacting on a patient's wellbeing, including long-term physical or psychological issues or death (range <1% to 44%). Diagnostic and medication-related incidents were most likely to result in harm and severe harm to patients.

Table 1 Three most common types of patient safety incidents in primary care, identified in the systematic review by Panesar et al. 2016

Administrative and communication incidents	**Diagnostic incidents**	**Prescribing and medication management incidents**
Administration incidents occurred in at least 6% of patient contacts. Related to: -Incomplete, unavailable, unclear or incorrect documentation -Inappropriate monitoring of laboratory tests -Insufficient communication between providers or between professionals and patients	Diagnostic incidents were responsible for 4% to 45% of all reported patient safety incidents. Related to: -Misdiagnosis -Missed diagnoses -Diagnostic incidents were most commonly associated with harm to patients, one study found that 58% of reported misdiagnoses were associated with harm (severity not described).	Prescribing and medication management incidence rate was between 1 and 90 out of 100 prescriptions (n=35 studies), being higher in the studies focusing on, e.g., older adults or those with polypharmacy. Related to (e.g.,): -Strength/dose -Dosage from -Length of treatment -Prescriptions without stating the daily dosage 8-11% of medication incidents were reported to result in harm (of any severity)

Safety of primary care compared to hospitals

In their systematic review, Panesar et al. (2016) indicated the frequency of patient safety incidents in primary care to be 2–3 incidents for every 100 consultations/records reviewed. The frequency is generally lower than the estimated 9-10% of patients experiencing adverse events in hospitals (de Vries et al. 2008; Schwendimann et al. 2018). However, the overall volume of people using primary care is notably higher than that of using hospital services in many parts of the world. Thus, even though the rate of incidents may be lower, this produces a considerable burden of harm globally (Panesar et al. 2016). Since the evidence on primary care safety is scarce, estimates should be treated with caution. They may underestimate the actual risk rate.

However, some important aspects need to be taken into consideration in Panesar et al.'s estimates. They defined patient safety incident as "any unintended or unexpected incident that could have or were judged to have led to patient harm". Within this broad definition, however, the authors chose to include only incidents of commission rather than omission (Sarkar 2016). Due to this, they counted events where the wrong course of action was undertaken, but they did not count events where the right course of action was not undertaken. Omissions are found to be a major cause for missed and delayed diagnoses (Singh et al. 2013), which Panesar et al. evidenced to be among the most harmful of primary care safety incidents. Therefore, this analysis likely shows us only the tip of the iceberg (Sarkar 2016).

Furthermore, in general, medication errors are not reported as systematically in primary care as in hospitals (Hakoinen et al. 2017;

Holmström 2017). Poor reporting leads to the underestimation of safety risks in primary care. For example, in Finland the system for reporting adverse events is mainly used in inpatient care institutions and it does not cover all outpatient care (Hakoinen et al. 2017, Holmström 2017).

2.3 MEDICATION SAFETY RISKS IN OLDER ADULTS IN PRIMARY CARE

Studies exploring safety of primary care have highlighted special patient groups carrying a higher risk for medication safety incidents. Those are older adults and patients taking multiple medications (Panesar et al. 2016; WHO 2017a). As the proportion of older population (≥65 years) is estimated to grow markedly, globally, during the following decades, the safety of their pharmacotherapy will become even more important (Mair et al. 2017).

The WHO has recently raised the coordination of care, polypharmacy management, and coordination of care for people with multiple illnesses as the key global challenges requiring solutions in medication safety (WHO 2017a, 2018, 2019).

The model below (Figure 3) summarizes key factors contributing to medication safety risks in older adults. The evidence for the model is derived from 1) the PCNE Classification for causes leading to drug-related problems (Pharmaceutical Care Network Europe Foundation 2017); 2) Basger et al.´s aggregated classification system for DRPs and their causes (Basger et al. 2015); 3) the synthesis of 1) and 2) by Dimitrow (2016) in her academic dissertation; 4) presentation of aspects in geriatric pharmacotherapy to consider in collaborative comprehensive medication reviews (Leikola 2012; Dimitrow 2016); and finally, 5) the WHO's reports "Medication Errors", "Multimorbidity" and "Administrative Errors" published in the Technical Series on Safer Primary Care (WHO 2016e, 2016g, 2016h).

The following chapters address medication safety risks presented in Figure 3, and potential tools to manage them as recommended by the WHO or other recognized organizations promoting patient and medication safety (National Institute for Health and Care Excellence 2015; WHO 2016g, 2017a; Scottish Government Polypharmacy Model of Care Group 2018; SIMPATHY 2019; WHO 2019).

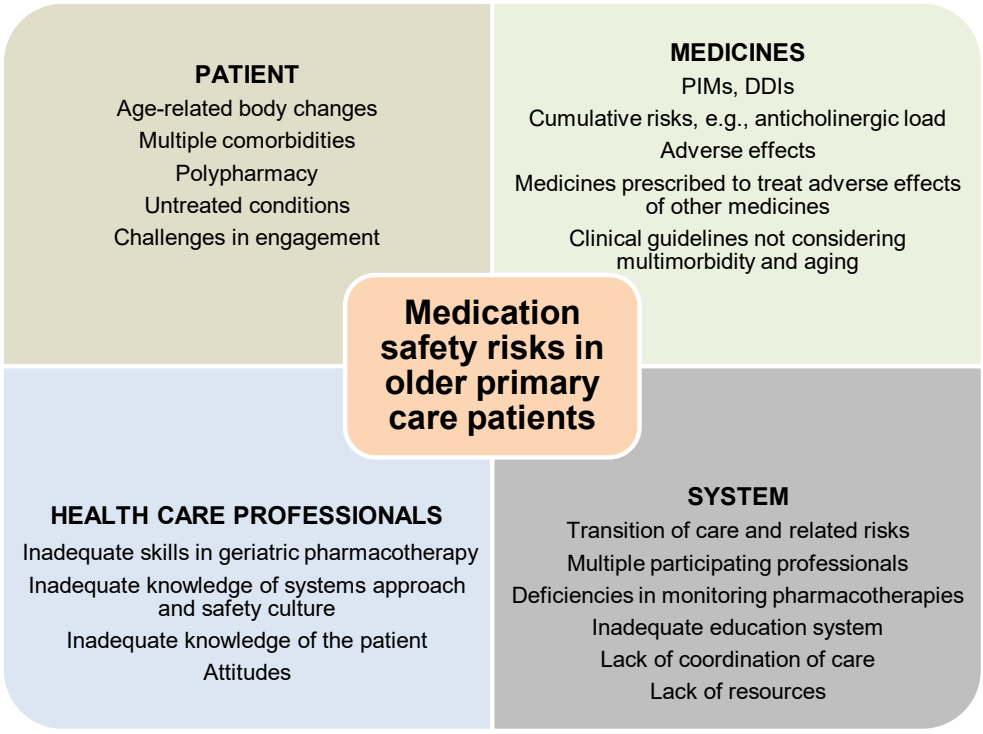


Figure 3 Factors contributing to medication safety risks in older primary care patients (based on and modified from Leikola 2012; Basger et al. 2015; Dimitrow 2016, WHO 2016e, 2016g, 2016h and PCNE 2017). PIM = potentially inappropriate medicine for older adults, DDI = drug-drug interaction

2.3.1 PATIENT-RELATED RISK FACTORS

Aging, multimorbidities and polypharmacy

Aging itself is a risk factor for medication safety. This is because aging is associated with several physiological changes that influence how medicines work in the body and thus how medicines should be used in older people. Aging also leads to impaired homeostasis and wide variability in drug response between individuals, which makes medicine dosing challenging (Hilmer et al. 2007). Furthermore, cognitive impairment is common. Despite these common features related to aging, older people form a heterogeneous group of population, each one having their own mixture of comorbidities and disabilities. It has been noted that comorbidities and disabilities correlate with age, therefore, older adults have been categorized as the young-old (65–74 years), the old-old (75–84 years) and the oldest-old (>85 years) (Bernabei et al. 2000). However, it is important to remember that the age does not directly indicate the health status of an individual old person, but it varies a lot between individuals.

Older people are prone to multimorbidity (co-existence of two or more chronic health conditions), which represents a major challenge in primary care, also concerning managing medications (Panagioti et al. 2015). In an extensive systematic review covering 75 publications from the years 2002–2015, patients with multiple long-term conditions and patients with mental-physical comorbidity were shown to be at heightened risk for patient safety failures, such as adverse drug events and medical complications, in primary care (Panagioti et al. 2015). Multimorbidity contributes to safety incidents which relate to the fact that patients may have to manage polypharmacy, even excessive polypharmacy. They may face difficult decisions about self-management without receiving the communication and support required with these demands (WHO 2016h). The frequency and complexity of their interactions with health care services, without coordination of care make them more vulnerable to failures of care (WHO 2016h).

Polypharmacy is increasingly prevalent (Saastamoinen and Verho 2015; Mair et al. 2017). E.g., in the USA, the prevalence of polypharmacy in older people has increased over time, and the national data indicate that approximately 39% of older people (>65 years) in the USA took five or more prescription medicines in 2011-2012 (Kantor et al. 2015). National data from the Irish Longitudinal Study on Ageing have reported polypharmacy ($\geq$5 medications) in 27% of the older population (>54 years) in 2017 (McGarrigle et al. 2017). Even though prevalence estimates vary across countries, polypharmacy in older people has been recognized as a major and growing public health concern worldwide (Mair et al. 2017; WHO 2019).

Discussions about reducing polypharmacy often suggest a distinction between appropriate and inappropriate polypharmacy (Garfinkel et al. 2015; Scott et al. 2015; Cadogan et al. 2016). Some authors have defined polypharmacy as the use of too many medications (Bushardt et al. 2008). Scottish Government Polypharmacy Model of Care Group has defined appropriate and inappropriate polypharmacy as follows (Scottish Government Polypharmacy Model of Care Group 2018):

Polypharmacy is appropriate , when (a) all medicines are prescribed for the purpose of achieving specific therapeutic objectives that have been agreed with the patient; (b) therapeutic objectives are actually being achieved or there is a reasonable chance they will be achieved in the future; (c) medication therapy has been optimized to minimize the risk of adverse drug reactions (ADRs); and (d) the patient is motivated and able to take all medicines as intended (Scottish Government Polypharmacy Model of Care Group 2018).

Inappropriate polypharmacy is present, when one or more medicines are prescribed that are not or no longer needed, either because: (a) there is no evidence-based indication, the indication has expired or the dose is unnecessarily high; (b) one or more medicines fail to achieve the therapeutic objectives they are intended to achieve; (c) one, or the combination of several medicines cause ADRs, or put the patient at a high risk of ADRs or because (d)

the patient is not willing or able to take one or more medicines as intended (Scottish Government Polypharmacy Model of Care Group 2018).

2.3.2 MEDICINE-RELATED RISK FACTORS

Due to age-related body changes, older adults are more prone to adverse effects of particular medicines than younger adults are. There is growing evidence that certain medicines and medicine groups are harmful (risks overweight benefits) in geriatric care and should be preferably avoided whenever possible, e.g., benzodiazepines, antipsychotics and strong anticholinergics (American Geriatrics Society 2019; Finnish Medicines Agency 2019). Since the 1990s, several explicit and implicit criteria have been established to guide and decrease prescribing of potentially inappropriate medicines (PIMs) for older adults (Spinewine et al. 2007a; Dimitrow et al. 2011; Lucchetti & Lucchetti 2017). One of the earliest, most well-known and widely used of these criteria is the Beers criteria (Beers et al. 1991) maintained by the American Geriatrics Society (AGS 2019). Beers criteria have also guided the Finnish national PIM database Meds75+, launched in 2010 and maintained by the Finnish Medicines Agency Fimea (Finnish Medicines Agency 2019).

Drug-drug interactions and cumulative risks (e.g., anticholinergic or serotonergic load of medicines) are identified challenges in older adults, particularly with polypharmacy (Auvinen et al. 2018; WHO 2019) Polypharmacy increases the risk for adverse effects (Gnjidic et al. 2012), which can be challenging to identify, and can be misdiagnosed as a new condition (Rochon & Gurwitz 1997). When this occurs, it can cause a prescribing cascade, where a new medicine is started to manage the adverse effect of another medicine (Rochon & Gurwitz 1997; Huh et al. 2019). Older people with polypharmacy have an increased risk of experiencing adverse effects, and thus prescribing cascades (Hilmer & Gnjidic 2009). The prescribing cascade, in turn, can increase the number of medicines used and contribute to overprescribing and medication-related burden (Mohammed et al. 2016).

Clinical guidelines are developed to enhance best evidenced care in diseases and to harmonize treatment practices. Thus, they are important tools in prospective medication risk management. Despite advances in pharmacotherapy, the availability of clinical guidelines for older adults with multiple morbidities is limited (Boyd & Fortin 2010; WHO 2019). In Finland, a wide range of disease-specific current care guidelines exist, but special current care guidelines on geriatric pharmacotherapy are missing (Kivelä & Räihä 2007; Dimitrow et al. 2013). Prescribing for multimorbid older adults is largely based on evidence-based guidance for single diseases, which does not generally take multimorbidity into account. This may lead to a situation in which patients are prescribed medicines recommended by a number of disease-specific guidelines which in combination makes the management of

any single disease or the whole medication challenging, and may even lead to patient harm (Molokhia & Majeed 2017; WHO 2019).

According to estimates, as many as 11% of unplanned hospital admissions are caused by medication-related harm, 70% of these incidents concerning multimorbid older adults with polypharmacy (Kongkaew et al. 2013). A recent study from Finland estimated that 23% of the unplanned geriatric hospital admissions resulted from adverse drug events (Laatikainen 2020).

2.3.3 HEALTH CARE PROFESSIONAL RELATED RISK FACTORS

A number of factors related to healthcare professionals have been identified to contribute to medication safety risks in older adults. Lack of interprofessional collaboration is a key challenges (Kallio et al. 2016;WHO 2016g; WHO 2016h). On the other hand, gaps in geriatric pharmacotherapy competences and skills affect all healthcare professionals and care provided in both primary and secondary care, as well as in social services such as nursing homes (Juola et al. 2015; Dimitrow 2016; WHO 2016g, Mononen et al. 2020).

In addition to geriatric pharmacotherapy, knowledge and understanding of the principles of systems-based risk management is essential. The following factors have been associated with health care professionals that may contribute to medication errors (WHO 2016g):

- Lack of therapeutic training
- Inadequate drug knowledge and experience
- Inadequate knowledge of the patient
- Inadequate perception of risk
- Overworked or fatigued health care professionals
- Physical and emotional health issues
- Poor communication between health care professionals and patients

In Finland, the current social and health care system does not have an appropriate, built-in system to ensure adequate competences of health care professionals. This also concerns adequate pharmacological knowledge, overall management of medication therapy and the safety culture, including application of risk management principles to pharmacotherapies (Hakoinen et al. 2017). Furthermore, there is no re-accreditation system in Finland; medical and other health care professionals are themselves responsible for engaging in life-long learning and continued education to keep up their competences (Keskimäki et al. 2019). According to the legislation, employers are responsible for providing professional training, though the implementation varies across health care organizations.

2.3.4 SYSTEM-RELATED RISK FACTORS

Systems thinking has been widely recommend as a preferable approach to manage patient and medication safety risks. This also applies to implementing

safe pharmacotherapy in older adults. This requires a good safety culture and leadership, a clear description of medication processes and responsibilities of professionals involved (Reason 2000; WHO 2017a, 2017b). Medication safety research has largely focused on describing errors – what kinds of errors occur and how many, where in the process, and for whom (Assiri et al. 2018). However, in order to develop the system, it is crucial to understand the underlying system-related factors. The WHO highlights the systems approach in developing safer health care, and has raised the following contributing factors associated with medication errors in primary care (WHO 2016e, WHO 2016g, WHO 2017a):

1) Contributing factors associated with the work environment (WHO 2016g)
- Workload and time pressures
- Distractions and interruptions
- Lack of standardized protocols and procedures
- Insufficient resources
- Issues with the physical work environment

2) Contributing factors associated with computerized information systems (WHO 2016g)
- Difficult processes for generating first prescriptions or repeat prescriptions
- Lack of accuracy of patient records

In Finland, the same kinds of system-related risk factors have been identified as contributing to medication safety risks in older patients (Kallio et al. 2016, Ministry of Social Affairs and Health 2018).

Medication discrepancies

Even though the importance of an accurate and reconciled medication list is acknowledged, many patients do not have such a list including all the medicines in use (Sinnemaki et al. 2014; Kekäle 2016; Schepel et al. 2019). The challenge is global and various procedures have been developed to address it (The European Union Network for Patient Safety and Quality of Care 2012; Kwan et al. 2013; WHO 2017a). The maintaining of an accurate medication list is challenging when various health care providers and organizations participate in the care of a patient (e.g., physicians with different specialties, from different public and private organizations). Non-prescribed medicines (OTC medicines), herbal products and food supplements are often missing from the lists even though they may have harmful interactions with the prescribed medications.

The prevalence of medication discrepancies have been studied especially in hospital settings, to occur in up to 70% of patients at discharge (Wong et al. 2008). In a Finnish study, discrepancies were found to occur in 73% of primary

care medication lists (n=174) (Pottonen 2014). In a study conducted in two emergency departments in the Helsinki University Hospital (HUS) and Kuopio University Hospital (KUH), discrepancies occurred with almost all of the patients (age ≥65 years, living at home and using ≥6 medicines): 100% of HUS (n=75) and 99% of KUH (n=75) patients had discrepancies in their admission medication charts (Schepel et al. 2019).

In Finland, this risk has been identified in the Rational Pharmacotherapy Action Plan (Ministry of Social Affairs and Health 2018). One of its primary goals is to ensure an accurate medication list for all medicine users. The mechanism for establishing the list will be built into the national patient data repository (Kanta), including prospective and retrospective data on electronic prescriptions (Kanta 2020). Since 2017, all prescriptions in Finland have been electronically managed via Kanta.

Deficiencies in monitoring pharmacotherapies

Monitoring of pharmacotherapies is an essential part of the medication use process and deficiencies in monitoring often stem from system-related factors. Without proper monitoring, the length of medication therapy may be unintentionally prolonged, the expected therapeutic effect may be suboptimal or medicines with clinically significant adverse effects are continued without proper assessment. This has been brought up in Finland, as well as globally (Panesar et al. 2016; WHO 2017a; Ministry of Social Affairs and Health 2018).

In primary care, nurses and practical nurses are often in charge of monitoring medication therapies (Dimitrow et al. 2014). In many organizations, particularly within home care and nursing homes, physicians meet the patients infrequently and mainly obtain information on a patient's health status and changes thereof from nurses. This leads to risk of missing information or changed information. For this reason, nurses need to be properly instructed to know precisely which issues to monitor with patients' medications and/or health status and why, and what to do if problems occur, e.g., when to consult the physician.

Community pharmacies could be more involved in the monitoring of medication therapies. They see people with chronic conditions at least every three months when refilling their prescriptions. These encounters could form regular checkpoints to be integrated in the patient's care path. Pharmacy owners have indicated willingness to build their capacities to this direction (Jokinen et al. 2019, Jokinen 2020). However, progress has been slow in Finland and elsewhere, despite the recognized need for improved monitoring of medication therapies to ensure desired treatment outcomes.

Lack of coordination of care

Challenges with coordination of care are significant system-related problems appearing in any health system, and are acknowledged globally (WHO 2018). Coordination of care, or care coordination, is defined by the WHO as "a proactive approach to bringing together care professionals and

providers to meet the needs of service users to ensure that they receive integrated, person-focused care across various settings" (WHO 2018). This means that patients' needs and preferences are known and communicated at the right time, to the right social/health care professionals, and that this information is used to guide the delivery of safe, appropriate, and effective care (The Agency for Healthcare Research and Quality 2018). Transitions of care are particular risks, often producing medication discrepancies (WHO 2016i).

In Finland, for example, the lack of coordination was identified as the major challenge in the National Medicines Agency's program to optimize medicine use in older adults (Kallio et al. 2016; Kumpusalo-Vauhkonen et al. 2016). The system-based factors were found to lead to a situation where no one in the care team can concentrate on an individual patient's medications. Such "dis-organization" is stated to be particularly challenging and risky for patients with a complex situation consisting of several chronic conditions, taking multiple medications, often prescribed by several specialists who are in little or no contact with one another — a recipe for pharmacological chaos (Avorn 2010).

A recent Canadian qualitative study reported on patient experiences, which well represents problems in care coordination (Ploeg et al. 2019). The experience of living with multiple chronic conditions is complex and multi-faceted. However, these patients often experienced the services to be piecemeal, focusing on single physical conditions rather than on the interaction of all their chronic conditions. They felt that health care professionals seldom attended to their holistic psychological and social needs as a person living with multiple chronic conditions.

Despite the challenges in the coordination of medication management processes in primary care, little research has focused on prospective medication risk management of older adults in this setting. Coordination of care of home-dwelling older adults has been studied from a nursing approach with various interventions focusing on disease management, transitional care and self-management education programs (Marek et al. 2010; Kim et al. 2016), though a prospective medication risk management approach has been out of their scope.

2.3.5 MEDICATION SAFETY IN HOME CARE

Most older people live on their own in their own homes. If their health condition and functional ability deteriorate, the first service option in primary care is often support by home care services. In Finland, 11% of those aged >75 years or over received regular home care services in 2018 (Finnish Institute for Health and Welfare 2019). The care in home care in primary care mainly relies on nurses and practical nurses with home visits. Frequency of home visits depends on client's need, varying from e.g., once a week to four times per day (Dimitrow et al. 2014; Keskimäki et al. 2019). Contributions of carers and family members are also important. Medicines for home care clients are

dispensed from community pharmacies: either the client, family member or practical nurse visits pharmacy. Medicines can also be supplied with automated dose dispensing in two-week period (Sinnemäki et al. 2014). This section discusses medication safety risks in older adults identified in the home care setting in primary care.

Medication safety research on older adults in primary care has focused on institutional settings, such as nursing homes (Storms et al. 2017; Devik et al. 2018). Home care clients live alone or with a spouse or other caregiver, which may contribute to different medication safety risks. A recent Norwegian study described and compared DRPs in older persons across nursing homes and home care (Devik et al. 2018). Significantly more DRPs were identified among patients receiving home care than patients living in nursing homes. While patients living in nursing homes were often undermedicated, documentation discrepancies were more common in home care (Devik et al. 2018).

Furthermore, home care personnel may face complex situations and have to make decisions on their own. They also carry a remarkable responsibility for the care, as the home care clients usually meet with their physician infrequently (Devik et al. 2018; Meyer-Massetti et al. 2018). Home care nurses and practical nurses are expected to monitor the benefits and risks of medications, to identify clinically significant DRPs and to communicate them to the physician. However, in many cases, their education and skills are not adequate to fulfill these demanding tasks (e.g., Mononen et al. 2020). This has led to the development of various DRP screening tools that assist in medication risk assessment (Dimitrow et al. 2014; Puumalainen et al. 2019).

Only few recent systematic reviews focus on home care patients' care in general (Kivimaki et al. 2019) or more specifically on their medications (Meyer-Massetti et al. 2018). Kivimäki et al. (2019) systematically reviewed literature on safety of older people at home (Kivimaki et al. 2019). They identified four dimensions of safety at home, namely 1) physical, 2) social, 3) emotional and mental, and 4) cognitive safety. However, the study did not consider medications.

Meyer-Massetti et al. (2018) evaluated evidence on the incidence and types of DRPs in home care (Meyer-Massetti et al. 2018). Altogether 44 studies were included in their systematic review, more than half (n=23) originating from the US. The most commonly reported DRPs were the use of PIMs, medication errors (mostly medication-related discrepancies), adverse events, and drug-drug interactions (Table 2). The study indicated a high frequency of DRPs among home care patients – up to 50% of patients being influenced by DRPs. The authors concluded that medication errors were more frequently reported in the home care setting compared to inpatient care.

Polypharmacy and increasing age of the patients were identified as risk factors for DRPs in home care settings (Meyer-Massetti et al. 2018). Polypharmacy was associated with an increased prevalence of medication discrepancies, DDIs and use of PIMs. Of the patients, only 48% were identified to have a reconciled medication list. The rate for adherence problems was 27%.

System-related factors, such as missing interdisciplinary team work and a lack of medication reviews, were also identified as contributors to DRPs (Meyer-Massetti et al. 2018). Home care providers were identified to often face acute medical situations where they have to make decisions independently. These situations often relate to care transfers that are rushed, resulting in limited time for adequate discharge planning. New enrollment in home care was associated with an increased risk for potential DRPs. Several health care visits and the use of several health care providers were associated with an increased risk for potential DRPs. Furthermore, patients and informal caregivers were identified to be critically important partners in medication use process which should be better taken into account.

Table 2 The most common types of DRPs identified among home care patients in a recent systematic review by Meyer-Massetti et al. 2018, covering 44 studies from the years 2000–2016

PIMs	Medication errors (MEs)	ADEs
• PIMS were the most frequently observed type of DRPs • 19.8–48.4% of home care patients were exposed to PIMs • Psychotropic medicines and opioids were more likely than other medicines to be associated with DRPs	• Medication discrepancies were found in 53.2–83.0% of patients; e.g., additional medication, continuation of a medication that had been discontinued, discrepancies in dose, frequency, dose reduction in renal insufficiency • Incorrect home care medication lists: 50% of patients • Inappropriate splitting of tablets: 21 out of 102 patients in one study • DDIs were rarely studied, once studied prevalence of 10%–57% was reported • 40% of MEs were found to clinically compromise treatment. Most of the MEs were considered preventable	• ADEs were identified in 8% of patients with a PIM • 2 % of home care patients had medication-related ADEs associated with hospitalization

Home care in Finland

In Finland, home nursing is provided together with home help services, forming an integrated service "home care" targeted to those unable to cope on at home on their own (Keskimäki et al. 2019). In 2018, 11% of Finnish older adults ≥75 years received regular home care services (Finnish Institute for Health and Welfare 2019).

Currently, home care services are primarily based on regular, usually daily, home visits of home practical nurses (PNs), coordinated by home care nurses. These personnel offer practical assistance with everyday tasks that extend to a range of medical nursing tasks, such as treating chronic ulcers and, administering medications. As practical nurses meet older home care clients

regularly, they have a good opportunity to identify and solve potential DRPs (Dimitrow et al. 2015).

However, they do not necessarily have online access to the health portal and patient records during the home visits to assist them in decision making and documenting observations on the health status of their clients. Usually they pass on their findings to the home care nurses, who pass the information to the attending physician. Physicians are responsible for medications of home care patients, and often they have to make treatment decisions without seeing the patient. The hierarchical flow of patient information can lead to situations where the information does not reach all professionals involved or the information content unintentionally changes along the way (Eloranta et al. 2009). It is likely that each participating professional interprets and communicates the information on the patient's situation according to own educational background and work experience.

The allocation of physicians' time for home care patients is limited in Finland. It is likely to become even more limited in the future, as the proportion of older adults of the entire population is growing (Official Statistics of Finland 2020). This is putting more pressures on developing new collaborative procedures for organizing home care, also managing medications. As part of re-organizing the care, PNs' involvement in monitoring medication risks and benefits could be enhanced. However, their enhanced participation requires changes in their knowledge and skills in applied geriatric pharmacotherapy (Dimitrow 2016, Mononen et al. 2020).

A need for enhancing pharmacists' involvement in medication management of older adults has been identified (Kumpusalo-Vauhkonen et al. 2016; Kallio et al. 2018). The Finnish Medicines Agency's interprofessional network study on medicines optimization of older adults stated that pharmacists have been missing from the primary care teams to this day, even they could contribute to the rational use of medicines (Kumpusalo-Vauhkonen et al. 2016). A stronger contribution by community pharmacies to medication safety in home care could be expected, as they dispense and dose dispense medicines to home care clients and have regular contacts with home care nurses. However, this potential is underused. The research and development projects have tried to enhance community pharmacists' involvement but the real breakthrough remains absent.

The Rational Pharmacotherapy Action Plan published in 2018 represents a remarkable recent milestone in improving coordination and integration between different health professionals involved in the medication use process (Ministry of Social Affairs and Health 2018). The need for pharmacists' contribution to regular medication reviews for older adults was highlighted. Pharmacists have improved their competences and skills required for comprehensive medication reviews during the last few decades, and established national recommendations for medication review competences for pharmacists working in community pharmacies as well as other health care settings in 2017 (AATE 2017). Since 2014, the pharmacy undergraduate

education has incorporated medication review competences in the BSc (Pharm) curriculum.

Clinical pharmacy services within home care – selected examples from the USA and Australia

Little research has focused on the involvement of pharmacists in the medication use process of home care clients. Available studies are mainly conducted in the United States and Australia (Reidt et al. 2014; Clark et al. 2016; Elliott et al. 2017). In these studies, the pharmacist has worked as a part of the home care team. In the global context, as well as in Finland, community pharmacists' contribution to medication use process of home care clients has been modest and focused mainly on medicine dispensing, DDI screening, automated dose dispensing and assisting in renewing prescriptions (Heikkilä et al. 2006; Jokinen et al. 2014; Sinnemaki et al. 2014; Kallio et al. 2018, Jokinen 2020). This chapter focuses on the potential benefits of adding a clinical pharmacist to the medication use process of home care clients.

Studies from Australia, the US and the UK have evidenced the need and favorable outcomes of adding a pharmacist in the home care team (Reidt et al. 2014; Clark et al. 2016; Dilks et al. 2016; Elliott et al. 2017).

Reidt et al., for example, developed a home care model in the US in which a pharmacist was a part of a home care team (Reidt et al. 2014). The pharmacist made home visits to reconcile and review medications for indication, effectiveness and safety (Reidt et al. 2013). After the home visit, the pharmacist contacted physicians to recommend changes to medication therapy. Recommendations to physicians included dose adjustments of medications, initiation of discontinuation of medications as well as laboratory monitoring of medications. The pharmacist then coordinated medication changes and care follow-ups with the client, caregivers, and the home care nurse.

Currently in the USA, it is mandated that clients referred to home health care services receive a comprehensive assessment from the service providing agency (Legal Information Institute 2019). The assessment also covers medication therapy and the content is defined as follows: "medication review of all medications the patient is currently using in order to identify any potential adverse effects and drug reactions, including ineffective drug therapy, significant side effects, significant drug interactions, duplicate drug therapy, and noncompliance with drug therapy".

In Australia, a study by Elliot et al. (2017) describes the successful development of a collaborative, person-centered model of clinical pharmacists' support for nurses and clients of a home nursing service that incorporates direct client care and indirect care (nurse support). The model is targeted to a group of community-dwelling older people known to be at high risk of medication-related problems and to have poor access to clinical pharmacy support (Elliott et al. 2017).

2.3.6 KEY SAFETY RISKS IN GERIATRIC PHARMACOTHERAPY IN FINLAND

In line with global findings, Finnish studies from medication error reporting systems (particularly HaiPro) and from the medication error cases investigated by the National Supervisory Authority for Welfare and Health (Valvira) indicate that older adults are most vulnerable to be harmed by medication errors (Linden-Lahti et al. 2009; Schepel 2018; Laatikainen 2020). PIMs are commonly used, particularly BZDs, antipsychotics and anticholinergics (Leikola et al. 2011; Saastamoinen & Verho 2015; Hyttinen 2018; Jalava et al. 2018; Kurko et al. 2018; Hyttinen et al. 2019). Furthermore, in Finland, nearly half of medication costs are produced by under 5% of medicine users (Saastamoinen & Verho 2013, 2015). These patients use the highest number of medicines and are older than other medicine users, with more than one-fourth of them being older than 75 years (Saastamoinen & Verho 2013). Therefore, knowing the medication safety risks for older adults is crucial, and thereafter developing strategies and tools for their prospective management. This chapter focuses on major policy initiatives and actions taken in Finland since 2006 to improve the quality of geriatric pharmacotherapy.

A milestone in the efforts to improve medication safety of older adults in Finland was the Ministry of Social Affairs and Health's report on the state of geriatric care in Finland in 2006 (Kivelä 2006). The report highlighted challenges in geriatric pharmacotherapy in outpatient and inpatient care, calling for urgent action. To tackle the challenges, MSAH established a working group (2006–2009) to improve the quality of geriatric pharmacotherapy. The working group summarized legal responsibilities for municipalities to ensure the safety of geriatric pharmacotherapy in outpatient and inpatient care (Ministry of Social Affairs and Health 2007). This municipal bulletin also contained an evidence-based list of safety issues requiring urgent action (Table 3) and recommended actions to take to manage them. The bulletin recommended, e.g., more undergraduate and continuing education in geriatric pharmacotherapy for physicians, nurses and practical nurses, a national interprofessional program to prevent harmful effects of pharmacotherapies in older adults and development of current care guidelines by adding specific information regarding the care of older people (MSAH 2007). Furthermore, annual collaborative medication reviews were recommended, and the role of pharmacies in medication counseling was emphasized. The working group also coordinated the development of guidelines for geriatric pharmacotherapy, which is still in use (Kivelä & Räihä 2007). Furthermore, the working group started the development of a national PIM database under ROHTO (Meds75+), currently maintained by Fimea (Finnish Medicines Agency 2019).

Has anything changed in geriatric pharmacotherapy since 2007?

In order to evaluate what has changed in the quality of geriatric pharmacotherapy since MSAH sent the municipal bulletin in 2007 a comparison was made between the outpatient medication risk list in 2007 and the current situation. The estimate of the current situation is based on the review of the recent national literature on geriatric pharmacotherapy, particularly in outpatient care.

The literature search revealed that the safety issues identified over 10 years ago are still evident and little progress has been made (Table 3). Recent studies indicate that we are still facing the same challenges as in 2006 (Pitkälä et al. 2015; Juola et al. 2016; Kallio et al. 2016; Hakoinen et al. 2017; Auvinen et al. 2018; Jalava et al. 2018; Kurko et al. 2018; Vartiainen et al. 2018). Use of benzodiazepines, antipsychotics, antidepressants, PIMs and the simultaneous use of $\geq$2 psychotropic medications, as well as high loads of anticholinergic and serotonergic medications, combined with the lack of coordination of care, remain still prevalent.

Dimitrow (2016) conducted a literature review on Finnish studies (published between January 1, 2000 and December 31, 2015) on medicine use known to be potentially harmful for older adults (Dimitrow 2016). Altogether 75 research articles were found. A majority (87%) of the articles focused on describing trends in medication use, polypharmacy and potentially inappropriate medicine use. A minority of the studies described interventions to solve these problems. It seems that there has been much discussion on the need for changes in geriatric care practices, while the actual changes and implementation of new practices are still either lacking or under way (Kumpusalo-Vauhkonen et al. 2016; Hakoinen et al. 2017; Ministry of Social Affairs and Health 2018). Furthermore, fewer research has focused on pharmacotherapy of home-dwelling older adults compared to institutional care (Dimitrow 2016). Research has also focused more on older patients with cognitive impairment such as Alzheimer's disease than on the mainstream of older people living at home on their own (Dimitrow 2016).

Table 3. Medication safety challenges in geriatric pharmacotherapy in older (≥65 years) outpatients highlighted in 2007 by the Ministry of Social Affairs and Health when calling for actions from municipalities to manage these challenges, compared to the current challenges as identified by the author of this thesis according to the recent literature from Finland

Medication safety challenges in outpatient geriatric pharmacotherapy highlighted in 2007 by the Ministry of Social Affairs and Health in its call for actions to municipalities (Ministry of Social Affairs and Health 2007)	**Current medication safety challenges with geriatric pharmacotherapy with home-dwelling older adults (based on studies published in 2015–2019)**
• Use of PIMs • Use of ≥2 psychotropic medications without appropriate diagnosis • Use of drugs with severe drug-drug interactions • Hospital admissions due to DRPs	• **Use of PIMS** ○ Auvinen et al. 2018 (baseline data collected in 2015-2016 in The Finnish Interprofessional Medication Assessment (FIMA) study, conducted in home care setting): The majority (87%) of home care patients (≥65 years) (n=512) had excessive polypharmacy (≥10 medicines). The most commonly used (97%) ATC medicine class was nervous system medicines. The use of medicines with anticholinergic (30%) or sedative (20%) properties was common. ○ Vartiainen et al. 2018 (data from the FIMA study, data collected in 2015-2016)*:* Use of PIMs (according to Meds75+) was common with home care patients (48% used), most commonly CNS medications (pregabaline, hydroxyzine, zolpidem) ○ Saastamoinen and Verho 2015: *(*national register study, data collected in 2011)*:* 31.4% of all older (≥65 years) medicine users (n=82,670) had a potentially inappropriate medicine while the proportion was 56.5% for those with high-cost excessive polypharmacy (10 or more medicines) (n= 64,612) (p<0.001). Prevalence of use of ≥3 psychotropics was 14%, chronic benzodiazepines 12%, long-acting benzodiazepines 4%, anticholinergic medicines 26.7%, and Beers criteria medicines 28% in the high-cost excessive polypharmacy group. • **Use of antipsychotics** ○ Jalava et al. 2018*:* a systematic review on studies using Finnish data and published in 2000-2015 (n=27): Of the home-dwelling aged, 3–14% used antipsychotics. The highest prevalence (22–32%) was observed among those with dementia. Approximately 40% of the institutionalized aged used antipsychotics, with no differences in use between people with or without dementia. Antipsychotics were mainly prescribed by general practitioners. • **Long-term use of benzodiazepines** ○ Kurko et al. 2018*:* national register study including all the purchases of benzodiazepines during years 2006 to 2014. .Long-term use of BZDs was still prevalent among older adults in 2014

	(Kurko et al. 2018), use was relatively more common in the older adults than in other age groups, even use was declining. • **Clinically significant DDIs, cumulative risks for adverse effects** o Auvinen et al. 2018, data collected in 2015-2016 in the FIMA study. Clinically relevant (SFINX record, Class C or D) drug-drug interactions were observed in 74% of the home care patients (n=512). The most frequent cumulative risks of adverse effects were risk of bleeding (66%), constipation (58%) and orthostatic hypotension (54%). Medicines affecting renal function were used by 85% of the patients.
Key challenges with organizing the outpatient medication use Key challenges relate to the overall responsibility for patient's care and to transfer of patient information • Lack on annual medication reviews for patients with long-term diseases/conditions • Regular use, or use on too long period of time of medicines meant to be used only for a short period of time or when needed (e.g., sleeping medicines, pain medicines) • Renewing of prescriptions without proper evaluation of the need to continue the drug treatment	**Key challenges with organizing the outpatient medication use** Key challenges relate to the overall responsibility for patient's care and to transfer of patient information • Kallio et al. 2016: No one takes the overall responsibility for individual patient's medication regimen (Kallio et al. 2016) • Lack of regular medication reviews (Kallio et al. 2016) • Kiiski et al. 2019: Need for developing medication review practices with better identification of patients needing medication reviews and with better implementation of medication review practices. • Mononen et al. 2020: The major development needs identified in the study were: poor access to patient information and its transfer in healthcare, particularly the lack of reconciled medication lists and electronic health records; (2) poorly functioning medication use process in home care and social care units; and (3) limited patient involvement in their care).

2.4 STRATEGIES TO MANAGE MEDICATION SAFETY RISKS IN OLDER ADULTS IN PRIMARY CARE

As the main safety risks in primary care relate to the care of multi-morbid older adults with polypharmacy, this chapter aims to introduce some approaches which have recently been recommended to be used to prevent, identify, and address these medication safety risks. Recent systematic reviews on interventions aiming to manage and optimize medicine use in older adults, and recent global guidance provided by the WHO and guidance at the EU-level or within EU-countries have been used in the selection of approaches and actions (National Institute for Health and Care Excellence 2015; Mair et al. 2017; Scottish Government Polypharmacy Model of Care Group 2018; SIMPATHY 2019; WHO 2019).

The following chapter (2.4.1) discuss approaches and interventions used to manage medication safety risks in older adults. Effectiveness of the interventions is discussed in Chapter 2.4.2.

2.4.1 MEDICINES OPTIMIZATION

Recently, progress in scientific research has notably extended the understanding of the pathophysiology of diseases which reflects the understanding of how medicines work in the body. With this knowledge, it is possible to customize medications according to each individuals' body function. Even though customized or personalized medication is usually associated with genomic information, there are many other aspects in pharmacotherapy that can be –and need to be – customized and optimized to improve treatment outcomes and reduce preventable risks and harms.

There is a growing international interest for summarizing evidence of medicines optimization and using this evidence for establishing recommendations and guidelines for implementing medicines optimization in clinical practice. For example, the UK National Authority for Healthcare Recommendation emphasizes not only system-based medication management but also the importance of personalized planning of of safe and effective medicines use (The King's Fund 2013; National Institute for Health and Care Excellence 2015).

Continuous weighing of patient needs, changing state of health and the benefits and disadvantages of medications are central for optimizing treatment (NICE 2015). International interest highlights the need for optimization, especially in older adults who are particularly a risk group for drug-related harm due to morbidity and aging (The King's Fund 2013; Mair et al. 2017; Scottish Government Polypharmacy Model of Care Group 2018; SIMPATHY 2019; WHO 2019). Therefore, their pharmacotherapy should be

'fine-tuned' more generally according to their individual needs. This applies to, e.g., adjusting the right dose and combination of medicines, duration of treatment, management of individual drug-related risks, including renal function, and choice of dosage form considering, e.g., problems of swallowing tablets (Figure 4).

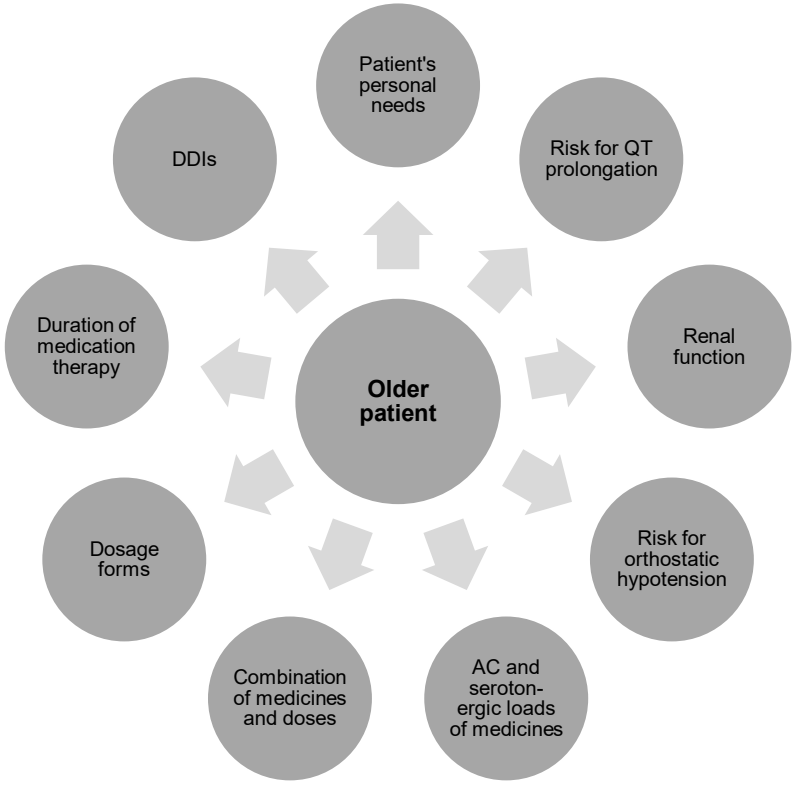


Figure 4 Examples of items to be considered and continuously re-evaluated when optimizing medication of an older patient. AC=Anticholinergic, DDI=drug-drug interaction

Medicines optimization process starts from the identification of the need for reducing medication-related risks, in which medication reconciliation, medication review and deprescribing processes are tools often used. Figure 5 presents aspects of medicines optimization.

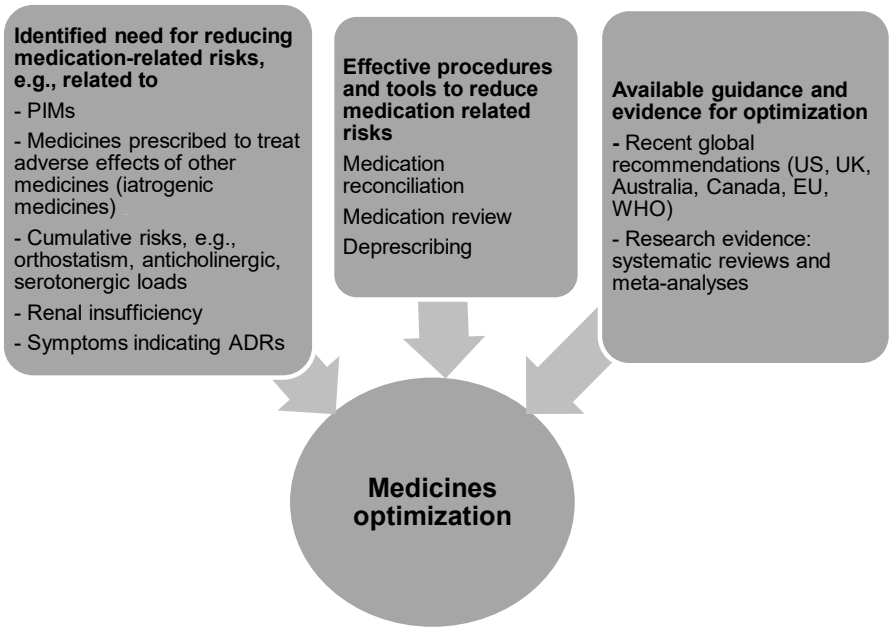


Figure 5 Identified needs for reducing medication-related risks, effective procedures and global recommendations form a framework for medicines optimization. PIM=potentially inappropriate medicine for older adults; ADR=adverse drug reaction.

2.4.1.1 Incorporating medicines optimization in medication management processes

Medication management and medicines optimization are key terms used when discussing appropriate medicines use. The main difference between medication management, or medicines management, and medicines optimization is the approach. Medicines optimization focuses on a single patient's medication, while medication management focuses on healthcare systems and processes (Royal Pharmaceutical Society 2013). Medication management is a key enabler for medicines optimization (National Institute for Health and Care Excellence 2015). Medicines optimization is defined as "a person-centered approach to safe and effective medicines use, to ensure people obtain the best possible outcomes from their medicines" (Royal Pharmaceutical Society 2013; National Institute for Health and Care Excellence 2015). As stated by the SIMPATHY consortium in the EU, these terms are often used in the same context together with the term "polypharmacy management". It relates to the whole systems approach for optimizing the entire care of multi-morbid patients through maximizing care benefits while reducing risks of inappropriate polypharmacy (Mair et al. 2017).

According to the WHO, the prevention of medication safety incidents and DRPs in older adults should be part of normal clinical practice, requiring, e.g., consideration of the patient's whole medication and health status as a part of prescribing, assessment of benefits and harms and critical assessment of the need for continuation of medicines used (Figure 6, WHO 2019). If the desired response is not achieved, or the medicine is useless, it is worth stopping medication, as unnecessary medication exposes older people to only unnecessary harm.

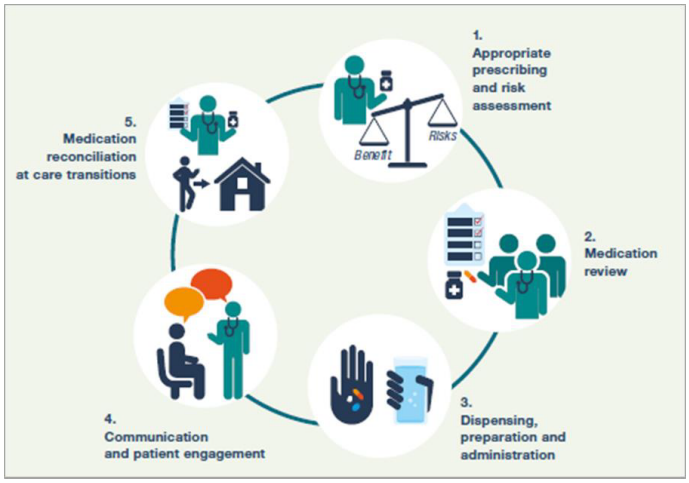


Figure 6 The WHO's key steps for ensuring medication safety in older adults (WHO 2019)

2.4.1.2 Initiatives in Europe on medicines optimization and polypharmacy management

As part of the Global Patient Safety Challenge: Medication without Harm, medication safety in polypharmacy was named as a key challenge (WHO 2017). Facing the challenge of reducing patient harm, the European Union (EU) issued a public health call to identify, develop and implement innovative solutions to address the problem of polypharmacy. Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly (SIMPATHY) was one of the projects funded to deliver tools to implement polypharmacy management programs throughout the EU in the context of quality, economic and political factors (SIMPATHY 2019). The Scottish Government markedly contributed to the work on polypharmacy management by, e.g., producing a practical guidance tool that helps health care professionals to work in partnership with patients when optimizing their medicines (Scottish Government Polypharmacy Model of Care Group 2018).

Further, in 2019, the WHO launched guidance particularly for polypharmacy management (WHO 2019). The technical report "Medication Safety in Polypharmacy" was published to support the goals of the third global patient safety challenge (WHO 2017; WHO 2019). This report outlines the polypharmacy challenge, the current situation, and key strategies to reduce medication-related harm in polypharmacy. The report has much in common with the report of the SIMPATHY project (Scottish Government Polypharmacy Model of Care Group 2018; SIMPATHY 2019).

In the UK, in 2013, The King's Fund published the paper "Polypharmacy and Medicines Optimisation – Making It Safe and Sound" (The King's Fund 2013). This paper outlined the view that polypharmacy is something to avoid. It proposed an alternative approach to the concept of polypharmacy: it may have positive (appropriate) or negative (problematic) potential. Reducing the number of medicines a person is taking, may not be the only factor to consider when reviewing polypharmacy; instead, optimization was highlighted. Some years later, The National Institute for Health and Care Excellence (NICE) published a paper "Medicines Optimization – the Safe and Effective Use of Medicines to Enable the Best Possible Outcomes," which is one of the first documents focusing particularly on medicines optimization (National Institute for Health and Care Excellence 2015). The paper highlighted the fact that continuous evaluation of patient needs, changing health situations, and the benefits and disadvantages of medication therapy are central to optimizing the treatment.

2.4.1.3 Optimization process as proposed by the Scottish Government

In line with the aims of the SIMPATHY project, the Scottish Government has developed a 7 Step patient-centered medicines review tool (Scottish Government Polypharmacy Model of Care Group 2018) (Figure 7). The tool helps in medicines optimization and provides a checklist for reviewing medicines by a pharmacist, physician, or nurse. The process is recommended to be started by a patient interview in order to identify and set objectives of drug therapy together with the patient and to evaluate the need of the medication, its effectiveness, safety, and efficiency for this particular patient, as well as the patient's willingness and capability to take the medicine. The process applies the principles of clinical interview (Kurz 2002; Guirquis 2012; Jyrkkä et al. 2017). The 7 Steps medication review procedure is included into the recent WHO polypharmacy guidance (WHO 2019).

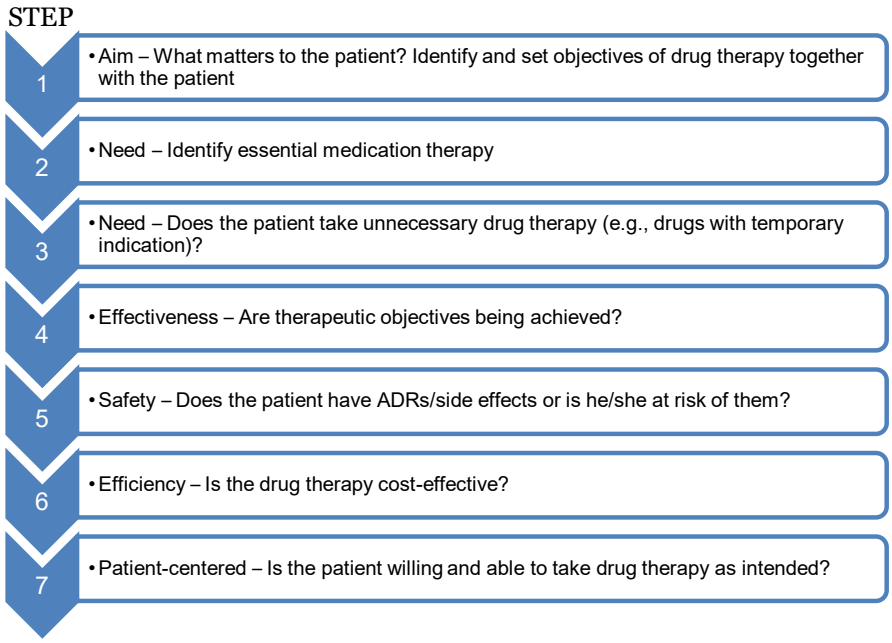


Figure 7 7 Steps medication review to optimize medicines, modified from the Scottish Government Polypharmacy Model of Care Group 2018

2.4.1.4 Medication reconciliation

An accurate medication list is a starting point for optimizing medicines. Medication reconciliation is the "process of identifying the most accurate list of all medications a patient is taking…and using this list to provide correct medications for patients anywhere within the health care system" (Institute for Healthcare Improvement 2011). The best possible medication history (BPMH) provides the cornerstone for medication reconciliation. The BPMH can be obtained through a systematic process by using a structured patient interview, and verification of this information with at least one other reliable source of information (e.g., a medication database, patient medication lists, a community pharmacy, or a primary care physician) (Kwan et al. 2013). Patients and their family members can be valuable and active participants in this medication history taking process by maintaining a current medicine list that is updated when any medicine changes occur (WHO 2017a).

2.4.1.5 Medication review

Medication review provides a method for a more comprehensive evaluation of the medication than medication history taking and reconciliation. Medication reviews are a tool for medicines optimization and prospective medication risk management (Hepler and Strand 1990). Medication reviews are among the

basic tasks of physicians, but collaborative medication reviews are becoming more common in many countries (Jokanovic et al. 2017). In the overview of systematic reviews, Jokanovic et al. have defined pharmacist-led medication review as a "systematic assessment of a consumer's medications and the management of those medications, with the aim of optimizing consumer health outcomes and identifying potential medication-related issues within the framework of the quality use of medicines" (Jokanovic et al. 2017). This definition is in line with the Pharmaceutical Society of Australia's definition for Home Medicines Review (HMR), the Medication Therapy Management (MTM) program in the United States, Clinical Medication Review in the United Kingdom, and Pharmaceutical Care Network Europe's (PCNE) definition of Medication review, as well as medication review practices in several other European countries (American Pharmacist Association and the National Association of Chain Drug Stores 2008; Pharmaceutical Society of Australia 2010; Blenkinsopp et al. 2012; Bulajeva et al. 2014; PCNE 2016; Griese-Mammen et al. 2018; Imfeld-Isenegger et al. 2019). Pharmacist-led medication review services are increasingly used with different variations and studied across the world (Bulajeva et al. 2014; Huiskes et al. 2017; Jokanovic et al. 2017; Imfeld-Isenegger et al. 2019; Kiiski et al. 2019).

Medication review procedures vary in terms of access to clinical data, patient, pharmacist and physician involvement and the purpose of the medication review (Bulajeva et al. 2014; Kiiski et al. 2016; Griese-Mammen et al. 2018; Kallio et al. 2018; Kiiski et al. 2019). Australia, the United States and the United Kingdom were the first countries to incorporate collaborative medication reviews into primary outpatient care, and the procedures in these countries are well-described in published literature (Burns 2005; Blenkinsopp et al. 2012; Leikola et al. 2012; Kiiski et al. 2016). In Europe, several countries are either developing or have recently implemented collaborative medication review procedures (Imfeld-Isenegger et al. 2019). Clyne's and PCNE's classifications of medication reviews are often applied to assess comprehensiveness of the procedures (Clyne et al. 2008; PCNE 2016; Griese-Mammen et al. 2018). According to PCNE, type 1 medication review is based on the medication history, type 2a is based on medication history and patient interview, type 2b on medication history and clinical data, and type 3 medication review is based on medication history, patient interview, and clinical data.

2.4.1.6 Deprescribing

Deprescribing has recently emerged as a new important action to be taken in medicines optimization (National Institute for Health and Care Excellence 2015). Most medicines do not need to be used lifelong (Duerden et al. 2013). Therefore, deprescribing is often needed to optimize medication therapy in medication review processes. Deprescribing is defined as "the process of withdrawal of inappropriate medication, supervised by a health care

professional with the goal of managing polypharmacy and improving outcomes" (Reeve et al. 2015).

Much advice and evidence is available when starting a new medicine, but far less information and evidence is available to support decisions to stop therapy (Duerden et al. 2013). Due to this, deprescribing has recently become the subject of intensive research internationally (Garfinkel et al. 2015; Reeve et al. 2015; Page et al. 2016; Farrell et al. 2018). Some countries have produced first-line guidance and tools for deprescribing (including the Deprescribing website in Canada, http://deprescribing.org/about/, and NICE 2015 in the UK). In Finland, deprescribing is mentioned as a tool to optimize medications in the recent Rational Pharmacotherapy Action Plan and its implementation roadmap by the Ministry of Social Affairs and Health (Ministry of Social Affairs and Health 2018, 2019).

Deprescribing can reduce the risk of adverse events such as medication-related hospital admissions, falls and decreased cognitive function (Woodward 2003; Page et al. 2016; Reeve et al. 2017). Despite the potential benefits, many barriers prevent physicians from deprescribing (Djatche et al. 2018). Identified key barriers include the fear of the recurrence of previous conditions for which a medication was initially prescribed and hesitance to deprescribe medications initially prescribed by another physician, particularly if there is limited communication between the physicians.

Furthermore, according to physicians, patient and/or caregiver belief in continuation of medications is a substantial barrier to deprescribing (Djatche et al. 2018). Moreover, the literature indicates that many patients and/or caregivers fear adverse drug withdrawal effects, and they believe there are more benefits than harms associated with their medications (Reeve et al. 2016). However, physicians' recommendations and support have a positive impact on patients' fears.

Based on the evidence emerging from randomized trials and observational studies, Australian medical researchers have developed a process for deprescribing (Reeve et al. 2014; Scott et al. 2015). The process includes a five-step approach:

(1) Consider all medications currently taken and the indication for each medication;
(2) Evaluate the overall risk of medication-induced harm in an individual person;
(3) Assess each medication for its potential to be deprescribed;
(4) Sort medications by the order of priority to deprescribe;
(5) Implement and monitor the deprescribing regimen.

These steps are described in more detail in Table 4.

Table 4 An example of a deprescribing protocol (modified from Scott et al. 2015)

Key steps	**Items to be considered**
1. Ascertain all drugs the patient is currently taking and the indication for each one	Ask patients (and carers) to bring all drugs (prescribed, over-the-counter, complementary and alternative medicines) and drug delivery aids to consultation or home visit. Ask patients (in a nonjudgmental way) about any regularly prescribed drugs not being taken and if so, why not (e.g., too expensive, adverse effects)
2. Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention	Assess risk according to -Drug factors: number of drugs, use of "high-risk" drugs, past or current toxicity -Patient factors: age >80 years, cognitive impairment, multiple comorbidities, substance abuse, multiple prescribers, past or current nonadherence
3. Assess each drug for its eligibility to be discontinued: -No valid indication -Part of a prescribing cascade -Actual or potential harm, a drug clearly outweighs any potential benefit -Disease and/or symptom control drug is ineffective or symptoms have completely resolved -Preventive drug is unlikely to confer any patient-important benefit over the patient's remaining lifespan -Drugs are imposing unacceptable treatment burden	Identify drugs being prescribed -For a diagnosis that is in doubt, i.e., not confirmed, highly atypical presentations; -For a confirmed diagnosis but in which evidence of efficacy is nonexistent; or which confer no additional benefit after a certain period of continuous use or after a certain age -Identify drugs prescribed to treat adverse effects of other drugs -Identify PIMs in older patients -Identify drugs contraindicated in particular patients (e.g., β-blockers in an asthmatic patient) -Identify drugs causing well-known adverse effects (e.g., constipation with calcium antagonists; postural symptoms with α-blockers) -Ask the patient how she/he feels about the medicines used (e.g., gained benefit, side effects, concerns) -Identify drugs unlikely to confer benefit over the patient´s remaining life span -Identify drugs that are particularly burdensome (e.g., difficulty swallowing tablets, monitoring requirements)
4. Prioritize drugs for discontinuation	Deciding the order of discontinuation of drugs may depend on integrating 3 pragmatic criteria: (1) those with the greatest harm and least benefit; (2) those easiest to discontinue, i.e., lowest likelihood of withdrawal reactions or disease rebound; (3) those that the patient is most willing to discontinue first Suggested approach is to rank drugs from high harm/low benefit to low harm/high benefit and discontinue the former in sequential order
5. Implement and monitor drug discontinuation regimen	-Explain and agree with patient on management plan -Discontinue 1 drug at a time so that harms (withdrawal reactions or return of disease) and benefits (resolution of adverse drug effects) can be attributed to specific drugs and rectified (if necessary) -Wean patients off drugs more likely to cause adverse withdrawal effects, instruct patient (or carer) on what to look for and report in the event of such effects occurring -Communicate plan and contingencies to all health professionals and other relevant parties (carers, family) involved in patient's care;-Fully document the reasons for, and outcomes of, deprescribing

Recent literature has also introduced the term “undiagnosing” which is defined as an approach considering the relevance of diagnoses (Page & Etherton-Beer 2019). The approach assesses whether the condition may have resolved or, represents normal aging and also the selection of individual targets. By undiagnosing conditions that are no longer relevant, medicines for the undiagnosed condition can correspondingly be deprescribed.

2.4.2 EFFECTIVENESS OF INTERVENTIONS TO IMPROVE APPROPRIATENESS OF MEDICINE USE IN OLDER ADULTS

A number of interventions have been developed and studied to improve appropriateness of medication use in older adults. This chapter summarizes the recent evidence of these interventions, based on the literature search conducted for this thesis in 2019. Systematic reviews and meta-analyses (n=9) published in 2015–2019 were included (Table 5).

According to this literature search, pharmacist-led medication reconciliations are effective in reducing medication discrepancies, and medication reconciliation programs during hospital transitions decrease ADE-related hospital revisits, all-cause re-admissions and emergency department visits (Mekonnen et al. 2016; Cheema et al. 2018).

Several recent systematic reviews and meta-analyses were found to summarize evidence on the effectiveness of collaborative medication reviews in various healthcare settings (Table 5) (Viswanathan et al. 2015; Kiiski et al. 2016; Jokanovic et al. 2017; Kallio et al. 2018). For example, in the overview of systematic reviews, Jokanovic et al. (2017) found several favorable outcomes with pharmacist-led medication reviews (Jokanovic et al. 2017). Primary studies reported positive impact on medication management, improvements in glycosylated hemoglobin, blood pressure, cholesterol and number and appropriateness of medications. Furthermore, a significant increase in quality of life was reported. However, medication reviews are often operationalized as isolated cross-sectional assessments of patients’ medications without proper integration and coordination with other patient care procedures, which has minimized their effectiveness (Huiskes et al. 2017). Furthermore, studies often lack descriptions of the procedures used (Kiiski et al. 2016, Kallio et al. 2018).

Page et al. (2016) studied the feasibility and effect of deprescribing in older adults on mortality and health in their systematic review and meta-analysis (Table 5) (Page et al. 2016). Deprescribing was not shown to significantly modify mortality in RCTs although nonrandomized data suggested that it reduced mortality. Mortality was significantly reduced when patient-specific deprescribing interventions were applied in RCTs.

Rankin et al. (2018) and Soler and Barreto (2019) in their research papers systematically summarized interventions aiming to enhance appropriate polypharmacy (Table 5) (Rankin et al. 2018b; Soler & Barreto 2019). It was uncertain whether pharmaceutical care improves medication appropriateness,

but may make little or no difference to hospital admissions or quality of life (Rankin et al. 2018). According to Soler and Barreto (2019), community-level pharmaceutical interventions can improve various clinical, epidemiological, humanistic and economic outcomes and potentially reduce risks associated with polypharmacy in the older population (Soler and Barreto 2019).

Table 5 Examples of recent (2015-2019) systematic reviews and meta-analyses of interventions aiming to optimize medicines use in older primary care patients

Reference	Aim of the study	Setting	Study design Number of studies	Provider and Intervention	Results and conclusion
Medication reconciliation interventions (n=2)					
Mekonnen et al. 2016	To Investigate the effect of pharmacist-led medication reconciliation programs on clinical outcomes at hospital transitions	Hospital transitions	Systematic review and meta-analysis including 17 studies (8 RCTs)	Pharmacist-led medication reconciliation interventions (telephone follow up/home visit, patient counselling or both during the first 30 days of follow-up)	Positive outcomes: decrease in ADE-related hospital revisits, all-cause readmissions and ED visits Conclusion: Pharmacist-led medication reconciliation programs are effective at improving post-hospital healthcare utilization and at improving medication safety
Cheema et al. 2018	To update the previous assessment of pharmacist-led medication reconciliation by restricting the review to randomized controlled trials (RCTs) only	Hospital setting	Systematic review and meta-analysis including 18 RCTs	Pharmacist's interventions included; medication reconciliation at admissions and discharge, tailored patient counselling, provision of telephonic consultation with patient's post-hospital discharge and creation of post-discharge medication lists	Conclusions: Pharmacists-led interventions were effective in reducing medication discrepancies
Medication review interventions (n=4)					
Viswanathan et al. 2015	To assess effectiveness of Medication Therapy Management (MTM) service interventions in outpatients with chronic illnesses. The article is based	Variety of outpatient settings (from and outside of the US) including community pharmacies, centralized	Systematic review and meta-analysis including 44 studies (21 RCTs, 4 non-RCTs, 19 cohort studies)	Pharmacist-provided interventions in outpatient care with the following pre-specified MTM intervention characteristics: a comprehensive medication review, patient-directed education, care	Main positive outcomes: MTM interventions improved medication appropriateness, adherence, and reduced medication dosing, reduced health plan expenditures on medication costs For patients with diabetes mellitus or heart failure, MTM interventions lowered the odds of hospitalization

Reference	Aim of the study	Setting	Study design Number of studies	Provider and Intervention	Results and conclusion
	on a systematic evidence report by the US Agency for Healthcare Research and Quality (AHRQ) to determine the effectiveness of outpatient MTM (Viswanathan et al. 2014)	pharmacies or pharmacy call centers, outpatient medical clinics, and patients homes. Excluded: MTM services provided within inpatient settings or shortly after hospital discharge		coordination, and opportunity for follow-up	However, the evidence from the studies was insufficient to determine the effect of MTM interventions on most evaluated outcomes (e.g., drug therapy problems, adverse drug events, disease-specific morbidity, disease-specific or all-cause mortality, and harms) Conclusion: Clinically effective MTM can either increase or decrease health care use and expenditures based on the needs of the patient
Huiskes et al. 2017	To assess effectiveness of medication review as an isolated short-term intervention (<3 months) irrespective of the patient population and the outcome measures used	Hospital pharmacy, physician clinics, and home care	Systematic review and meta-analysis of 31 RCT studies	Pharmacist, nurse or physician provided medication reviews irrespective of patient population	Positive outcomes: An effect was found on most drug-related problems: medication review resulted in a decrease of drug-related problems, more changes in medication (dose decrease, greater decrease or small increase in number of drugs) and reduces the number of falls Negative outcomes: No effect of medication review was found on clinical outcomes (mortality, hospital admissions/healthcare use, the number of patients falling, physical and cognitive functioning), quality of life and economic outcome measures
Jokanovic et al. 2017	To critically evaluate published systematic reviews relevant to pharmacist-led medication reviews in community settings	Community pharmacy	Overview of systematic reviews (n=35) Of these, 24 were of moderate and seven of high quality and were included in the data synthesis.	Pharmacist-led medication reviews	Positive outcomes: Results from the meta-analyses (performed in 12 systematic reviews) indicated positive impacts on glycosylated hemoglobin, blood pressure, cholesterol, and number and appropriateness of medications. Of the primary studies, favorable outcomes were demonstrated for diabetes control (78% of studies reporting the outcome), blood

Reference	Aim of the study	Setting	Study design Number of studies	Provider and Intervention	Results and conclusion
					pressure control (74%), cholesterol (63%), medication adherence (56%) and medication management (47%). Significant reductions in medication and/or healthcare costs were reported in 35% of primary research studies
Kallio et al. 2018	To identify medication review interventions for older adults involving community pharmacists and evidence of outcomes of these interventions	Articles involving community pharmacists in medication reviews for outpatients aged 65 and older were included	Systematic review of 16 articles	Community pharmacists provided medication review interventions, of which 6 were compliance and concordance reviews, 4 were clinical medication reviews, and 2 were prescription reviews Community pharmacists' contributions to reviewing medications varied from sending the dispensing history to other healthcare providers to comprehensive involvement in medication management	Positive outcomes: The most commonly assessed outcomes of the interventions were medication changes leading to reduction in actual or potential drug-related problems (n=12) and improved adherence (n=5). Medication review interventions seemed to reduce DRPs and improve medication adherence. Conclusion: Better designed, rigorous studies with more sensitive and specific outcomes measures are needed to assess the effect of community pharmacist contributions to reviewing medications.
Deprescribing interventions (n=1)					
Page et al. 2016	To determine whether deprescribing is a safe, effective, and feasible intervention to modify mortality and health outcomes in older adults	Older adults across all settings and medications	Systematic review and meta-analyses including 132 studies, of which 56 were RCT studies	Various deprescribing interventions by a health care professional (physician, pharmacist, nurse or multidisciplinary team)	Outcomes/conclusions: Deprescribing to reduce polypharmacy was not shown to significantly modify mortality in RCTs although nonrandomized data suggested that it reduced mortality Mortality was significantly reduced when patient-specific deprescribing interventions were applied in RCTs Deprescribing appeared to be feasible and generally safe

Reference	Aim of the study	Setting	Study design Number of studies	Provider and Intervention	Results and conclusion
Other types of interventions (n=2)					
Rankin et al. 2018	To determine which interventions, alone or in combination, are effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people	Interventions were provided in a variety of settings and were conducted in high-income countries.	Systematic review (Cochrane Review) including 32 studies, (18 RCTs, 10 cluster randomized trials, two non-randomized trials and two controlled before-after studies)	Interventions were delivered by healthcare professionals such as general physicians, pharmacists, and geriatricians. One intervention consisted of computerized decision support (CDS); and 31 were complex, multi-faceted pharmaceutical-care based approaches.	Outcomes/conclusions: It was uncertain whether pharmaceutical care improves medication appropriateness or reduces the number of potentially inappropriate medications (PIMs). Pharmaceutical care interventions may make little or no difference in hospital admissions or in quality of life
Soler and Barreto 2019	The objective was to summarize evidence on the effectiveness of community-level pharmaceutical interventions to reduce the risks associated with polypharmacy in the population over 65 years of age.	Community level pharmaceutical interventions	An overview of systematic reviews, including 16 studies (1 overview of systematic reviews, 12 systematic reviews, and 3 economic evaluations)	The categories of interventions included were: -Professional (review of drug use, educational interventions targeted at prescribers or users/caregivers) -Organizational (use of Information and/or communication technology, like screening tools or clinical decision making support) -Regulatory: regulation of prescribing practices -Financial: incentive programs to change prescribing practices -Multifaceted interventions	Positive outcomes: The interventions included demonstrated the benefits of pharmaceutical interventions for improving outcomes in the elderly over 65 years. The reported positive outcomes included reduction in PIMs, DDIs and improved use of appropriate and safe medications, improved adherence, and reduced ADEs, ADRs, DDIs, and drug-related negative health outcomes. Decreased drug costs and hospital admissions were also reported. Conclusions: Pharmaceutical interventions can improve various clinical, epidemiological, humanistic and economic outcomes and potentially reduce polypharmacy-related risks.

2.4.3 METHODOLOGICAL ASPECTS WITH INTERVENTIONS AIMING TO ENHANCE MEDICATION SAFETY IN OLDER ADULTS

Recently, several systematic reviews have been published which combine evidence of the effectiveness of interventions to optimize medication treatment in older adults in outpatient care (Table 5). The following chapters describe the key methodological aspects that should be considered when planning and conducting interventions and evaluating their effectiveness.

2.4.3.1 Selection of study design

Intervention study designs are often used to develop new approaches in health care services. There are several different study designs for intervention studies, of which the randomized, controlled trial (RCT) study design provides the most reliable information on the effectiveness of the intervention. However, when applied to the daily life of health care, the effectiveness of the intervention may seem very different. This is influenced by a number of confounding factors which are part of real-life in clinical practice and may be due to a variety of operating, professional and patient factors (Ford & Norrie 2016).

Recent research and methodological discussion has revolved around pragmatic trials, which, from the outset, begin to develop an approach to normal clinical life (Ford & Norrie 2016). Pragmatic trials represent the real world better than RCTs, due to including complex interventions, sometimes consisting of several interacting components and often involving the skills and experience of one or more health care professionals to deliver the intervention.

2.4.3.2 Selection of primary and secondary outcomes

Due to the above mentioned challenges, the outcome measures for the effectiveness of interventions aimed at rationalizing medication use in older adults require a special remark. The set of outcome measures should be made up of a variety of measures assessing potential changes in the safety/appropriateness of medication, clinical health status and possibly health service utilization and cost (Kozma et al. 1993).

Kiiski et al. carried out a systematic review of the interventions and related outcomes used to optimize medications of older adults (Kiiski et al. 2016; Kallio et al. 2018). The included studies used a variety of different outcome measures, which were summarized according to the ECHO (Economic, Clinical, and Humanistic Outcomes) model (Kozma et al. 1993) (Table 6). The systematic review showed that a wide variety of outcomes and outcome measures have been used in studies without being always optimally selected. Measuring the number of medicines in use alone does not make sense, since

underuse has also been observed in the older population with polypharmacy, and its correction increases the number of medicines. Furthermore, monitoring the direct cost of medicines is not always reliable. There is also a risk of misinterpretation when measuring the use of health services. Especially at the outset of medication optimization, more physician visits may be needed related, e.g., to deprescribing or individualizing the dose.

These various challenges make it difficult to demonstrate the effectiveness of interventions aimed at optimizing the medication of the patients, and to compare and compile results in systematic reviews and meta-analyzes. They also make it more difficult to convince policy makers to implement new policies and practices that may require resources and funding.

The Core Outcome Measures for Effectiveness Trials (COMET) initiative has proposed the development and reporting of a core outcome set (COS) as a solution to the challenge of measuring outcomes (Williamson et al. 2012; Prinsen et al. 2014). A COS is an agreed-upon standardized set of outcomes that should be measured and reported as a minimum in all trials in a specific clinic area (Williamson et al. 2012). In line with this, two recent Delphi studies have developed core outcome sets for trials aimed at improving the appropriateness of polypharmacy in older adults (Beuscart et al. 2018; Rankin et al. 2018a). Themes included in both COSs relate to medication-related outcomes, adverse effects or harm, clinical outcomes and patient-related outcomes. The sets are quite similar; there are differences between some specific outcomes and in the number of themes (Table 7).

Table 6 Outcome measures used in the medication review interventions for older adults, presented in the systematic review of Kiiski et al. (Kiiski et al. 2016, Kallio et al. 2018). The systematic review included 16 studies of which 5 were randomized clinical trials (RCTs)

Outcome measures	Main outcomes according to significance
CLINICAL OUTCOMES	
RCTs (n=5) <u>Indirect measures</u> Pharmacist recommendations and their acceptance (n=4) Medicine use and changes to medications (n=3) Sign and symptom control (n=2) Participant knowledge of medicines (n=2) Adherence to dosage regimens (n=2) Problems with medicines (n=1) Medication Appropriateness Index (MAI) (n=1)	**Significant outcomes** • More medicines started in the control group (n=1) • More changes to medications in the intervention group than in the control group (n=2) • Intervention participants more adherent than controls (n=1) • MAI improved in the intervention group (n=1) **Significance not reported** • 44% (17–72%) of pharmacist recommendations accepted or partially accepted (n=4) • More changes to medications in the case-conference group than in the written feedback group (n=1) • Better control of medications in the intervention group (n=2) • Intervention participants more adherent than controls (n=1) • Fewer problems with medicines in the intervention group than in the control group (n=12) • 60.8% (n=5,124) of participant problems (n=5,204) identified led to positive outcomes (n=12)
Other studies (n=11) <u>Direct measures</u> Falls (n=1) Pain (n=1) <u>Indirect measures</u> Pharmacist recommendations and their acceptance (n=6) DRPs (n=4) Medicine use (n=2) Adherence (n=3) PIMs (n=2) Medication Appropriateness Index (MAI) (n=1) Drug Burden Index (DBI) (n=1)	**Significant outcomes** • Fewer falls (n=1) • Pharmacists identified more recommendations (than computerized screening tool) in the case-conference group (n=1) • DRPs (forgetfulness, DDIs, intermittent drug intake) decreased (n=1) • Median number of regular prescribed medicines fell from 6 to 59 (n=1) • Better adherence to medication (n=1) • Percentage of participants with nonadherence fell from 38% to 14% (n=1) • MAI scores lower after intervention (n=1) • Reduction in sum of total of DBI scores for all participants (n=1) **Significance not reported** • 613 recommendations; 502 to participants (76% accepted), 247 to physicians (72% accepted) (n=1) • Physicians accepted 55% of pharmacist recommendations (n=1) • Pharmacists made 142 recommendations to prescribers in 110 participants (n=1)

	• 559 DRPs in 145 participants: 40% of DPRs resolved, controlled or improved (n=1) • 785 potential DRPs (6.5/participant): 51% (n=5,403) resulted in change of drug therapy (n=1) • Number of participants with 1 DRPs decreased from 94% to 58% (n=1) • Intervention led to decrease in PIMs (n=2) • Better adherence (n=23) **Nonsignificant outcomes** • Pain scores increased (n=1) • More recommendations to GPs in case-conference group than in written feedback group (n=1) • Self-reported ADRs decreased (n=1)
HUMANISTIC OUTCOMES **RCTs (n=5)** HRQoL (SF-36) (n= 3) Satisfaction, perceptions (n=2) **Other studies (n=11):** Perceptions, opinions (n=3) Ways to improve treatment review method (n=1) HRQoL (EQ-5D-5L) (n=1)	**Significant outcomes** • HRQoL: emotional role and social functioning reduced (n=1) • HRQoL: physical functioning and vitality improved in the control group (n=1) • Intervention group more satisfied with services than the control group (n=1) **Significance not reported** • All participants rated services excellent or good (n=1) • Pharmacists and GPs had positive opinion of pharmaceutical care (n=2) • HRQoL declined in the intervention group (n=1) **Nonsignificant outcomes** • HRQoL declined in general, nonsignificant differences between control and intervention groups (n=1) **Significant outcomes** • HRQoL improved (n=1) **Significance not reported** • Pharmacists concerned that they lacked skills and confidence, not mandated to take this role (n=1) • GPs attributed different values to outcomes and use of resources, leading to continuum between positive and negative responses(n=1) • Healthcare professionals were more positive about process of treatment review presented personally (n=1)

ECONOMIC OUTCOMES	
RCTs (n=5) Cost of medication (n=3) Cost of intervention (n=2) Time (n=2) Number of participant contacts with healthcare professionals (n=2) Hospitalization (n=2)	**Significant outcomes** • Pharmacists in the case-conference group spent more time on intervention than those in the written feedback group (n=1) **Nonsignificant outcomes** • Differences in total cost for the intervention and control groups (n=3) • Lower costs of prescribed medicines in the intervention than control group (n=1) • Fewer intervention participants hospitalized (n=1)
Other studies (n=11) Time (n=2) Cost of medication (n=1) Cost of intervention (n=1) Cost per QALY (n=1) Billing of process made by GPs as marker of completion of Home Medicines Review process (n=1)	**Significant outcomes** • Time to complete process reduced from median of 56 days to 20 days (n=1) • Average cost of medication for 28 days fell from £51,12 to £44,55 (n=1) **Significance not reported** • Pharmacists spent more time on intervention than GPs did (n=1) • Case conference group required more time than the written feedback group(n=1) • Support program resulted in projected savings of £52 per patient per year (n=1) • Cost of intervention estimated to be £98.72 per participant; probability of being cost-effective was 13.8% (n=1) • Cost per QALY estimates ranged from £11,885 to £32,466 depending on assumptions (n=1) • Potential financial saving of AUS$17,374 during postintegration phase (n=1)

Table 7 Two Core Outcome Sets (COSs) developed using the Delphi method for effectiveness trials aimed at improving the appropriateness of polypharmacy in older people in primary care (Beuscart et al. 2018; Rankin et al. 2018b)

	Beuscart et al. 2018		**Rankin et al. 2018**	
Theme	**Outcome**	**Definition**	**Outcome**	**Definition**
Medication-related outcomes	Potentially inappropriate medications	Drugs with risk of adverse drug reactions exceeding their expected clinical benefit to patients, particularly when safer therapeutic alternatives are available to treat the same condition	Medication appropriateness	Where medicines have been prescribed in accordance with the best available evidence and are suitable for a patient taking their medical history and co-morbidities (i.e., the presence of one or more medical condition) into consideration. As measured by a validated assessment of prescribing appropriateness (e.g., STOPP/START criteria or Beers criteria)
	Clinically significant DDI	A clinically significant DDI is defined as having a significant severity rating according to the drug interaction compendia used in the study (e.g., Drug Interaction Facts or Micromedex)	Clinically significant DDIs	The effect of a drug can be changed by another drug, herbal medicines, food or drink and this can lead to a change or complication in the patients' condition
	Underuse	A failure to prescribe drugs that are indicated, including (1) omission of an evidence-based drug; (2) too short a duration	The number of regular medicines prescribed	The total number of 'regular' medications that a patient has been prescribed (i.e., a prescribed medication that is scheduled or part of a repeat prescription), which would not include over-the-counter and herbal products if used regularly
	Overuse	The use or prescription of more drugs than clinically needed, including (1) any drug prescribed or used without an evidence-based clinical indication; (2) therapeutic duplication; (3) medication prescribed or used beyond the recommended duration	Therapeutic duplication	Therapeutic duplication describes a situation where a patient is prescribed two (or more) medicines of the same drug-class/pharmacological class, (e.g., a patient is prescribed two beta-blockers at the same time) which may increase the risk of adverse events
			Medication regimen complexity	A measure of how complicated patients find taking their medicines such as the number of medicines, how often they need to be taken and how they should be taken
			Medication side effects	A side effect can be described as an undesirable effect of a medication, either when taken or when it is withdrawn (stopped)
			Prescribing errors	Errors made in the prescribing of patients' regular or 'when required' medication

			Adherence	The extent to which a patient's medication-taking corresponds to agreed recommendations from a healthcare provider
Adverse effects or harm	Drug-related hospital admissions	Hospitalization due to an adverse drug reaction or medical error related to overuse, underuse or misuse of medications and which is the main reason for or contributes to hospital admission of a patient	Falls	An unexpected event in which the patient comes to rest on the ground, floor or lower level
			Serious adverse drug reactions	Any unexpected effect of treatment that results in death, or is life-threatening, requires admissions to hospital or a longer than expected hospital stay, or results in disability
Patient-related outcomes	Health-related quality of life	Personal health status: HRQoL usually refers to aspects of our lives that are dominated or significantly influenced by our mental or physical well-being	Cognitive functioning	Patients' cognitive function (e.g., memory, attention, language, confusion, reasoning, orientation to time and place)
	Pain relief	Whether pain has improved over the course of the trial	Quality of life	The standard of health, comfort and happiness experienced by an individual, including quality of life relating to medication use
			Patient perception of treatment (or medication) burden	An individual's perception of the effect on functioning and wellbeing that may be caused by exposure to treatment including the use of many medicines (polypharmacy)
Clinical outcomes			Mortality (all cause)	The death of a patient for any reason
Healthcare utilization			Hospitalizations	Admission or re-admission to hospital for treatment or monitoring
Knowledge			Patients' knowledge	Patients' knowledge of their medication and/or condition

2.5 A SYSTEMATIC REVIEW: DRUG-DRUG INTERACTIONS IDENTIFIED IN COMMUNITY PHARMACIES

2.5.1 INTRODUCTION

Drug-drug interactions (DDIs) are the first system-based medication safety risk that have been addressed in health care for a long time. Since the 1960s the importance of DDIs has increased over time due to the increased use of medicines and polypharmacy, which has increased the risk of DDIs. On the other hand, research evidence about DDIs has increased and has been utilized in DDI electronic alert systems. In the USA, for example, such systems have been in use for decades (also by consumers) (Greenlaw & Zellers 1978). In Finland, the first electronic medication risk management tools were designed for DDI risk management, and community pharmacies have been actively implementing these tools at the forefront of health care. The first screening tools were launched in community pharmacies in early 2000 (Toivo et al. 2005; Heikkila et al. 2006).

Existing studies on DDI incidence has focused on interactions in hospitalized patients (Laine et al. 2000; Reimche et al. 2011; Gonzaga de Andrade Santos et al. 2020). Studies have also focused on certain patient groups, e.g., aged people or cancer patients (Obreli Neto et al. 2012; van Leeuwen et al. 2013; Sanchez-Fidalgo et al. 2017) or on certain medicine groups, such as HIV drugs (Evans-Jones et al. 2010; Molas et al. 2018). A patient's age, number of prescribers involved and polypharmacy significantly increases the risk for drug-drug interactions (Sanchez-Fidalgo et al. 2017; Andersson et al. 2018). Less is known regarding DDIs in outpatients, particularly how community pharmacists could contribute to DDI management by applying their surveillance systems to the identification of high-risk medications.

The aim of this study was to systemically review the literature of existing studies on the incidence and prevalence of DDIs in outpatients, and particularly studies on DDIs identified in community pharmacies.

2.5.2 SEARCH STRATEGY

The Medline (Ovid) and Scopus databases were searched from January 1, 1995 to September 25, 2015 (Table 8). The literature search was updated on December 17, 2015. The systematic review was conducted applying the PRISMA guidelines (Moher et al. 2015).

The literature search process was conducted with the help of an information specialist at the Medical Library, University of Helsinki. In PubMed, MeSH (Medical Subject Headings) terms were used and all fields

were searched. In Scopus, the following fields were searched: title, abstract and keywords. To avoid searching for duplicates in Scopus, the search was filtered with "AND NOT INDEX (MEDLINE)".

Table 8 Databases and search terms used in the systematic literature search

Databases	Medline (Ovid Medline and Ovid Medline In-Process & Other Non-Indexed Citations) Scopus (Elsevier)
Search terms	**Related to DDIs** (OR search): drug interactions, drug* or medic* interact*, ddi **Related to outpatient care** (OR search): outpatients, ambulatory care, outpatient* or ambulatory*, communit* pharma*, primary health care, primary healthcare, primary care Main themes were combined with AND search
Filters	Publication date from 1995/01/01 to 2015/09/25

2.5.2.1 Inclusion and exclusion criteria

Studies describing the incidence or prevalence of DDIs in outpatients and which included all their medication were included (Table 9). Studies describing the incidence or prevalence of DDIs in hospitalized patients were excluded, as well were studies focusing on DDIs of certain drugs (e.g., warfarin, antineoplastics, HIV drugs) or on specific patient groups (e.g., HIV patients, cancer patients). Articles were included if written in English and if full-text version was available through the University of Helsinki Library.

Table 9 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Patients (P)	• Outpatients • Studies including patients of all ages, or older adults (≥ 60 years) • Number of dispensed prescriptions or medicines used not defined or ranged	• Inpatients, hospitalized patients • Studies focusing on DDIs of certain drugs (e.g., warfarin, antineoplastics, HIV drugs) or on specific patient groups (e.g., HIV patients, cancer patients) • Number of dispensed prescriptions or medicines used ranged other than ≥2
Methods	• Any study design, excluding narrative reviews	• Narrative reviews
Outcome (O)	• Prevalence or incidence of DDIs is presented	• Prevalence or incidence of DDIs is not presented
Time frame (T)	• Publication date from Jan 1, 1995 to Sep 25, 2015	• Publication date outside of the presented time frame

2.5.2.2 Selection of the studies

The titles and abstracts of the studies were read by authors TT and EN (author of the thesis and Emmi Nieminen). Studies were selected based on the title and abstract. Reference lists of the included studies were reviewed and studies that met the inclusion criteria were included.

Full-text articles were read, and the following data were extracted and analyzed qualitatively: country of origin; study design and setting; cohort or sample; DDI screening tool and DDI categorization used; prevalence or incidence of DDIs; identified risk factors for DDIs; the most prevalent DDIs and drugs involved. A detailed summary table of the included studies was made.

2.5.3 RESULTS

2.5.3.1 Included studies

The literature search produced 2,333 research articles. The study selection process is shown in Figure 8. In total, 34 studies described DDIs in an outpatient setting. Of these, nine studies were conducted in community pharmacies and used data from dispensed prescriptions (Buurma et al. 2006;

Heikkilä et al. 2006; Cremades et al. 2009; Chatsisvili et al. 2010; Vaidhun and Satnish 2011; Bucsa et al. 2012; Obreli-Neto et al. 2012b; Nicolas et al. 2013; Dirin et al. 2014). The studies reporting DDIs identified in the prescriptions dispensed from community pharmacies (n=9) are presented in this thesis (Table 11).

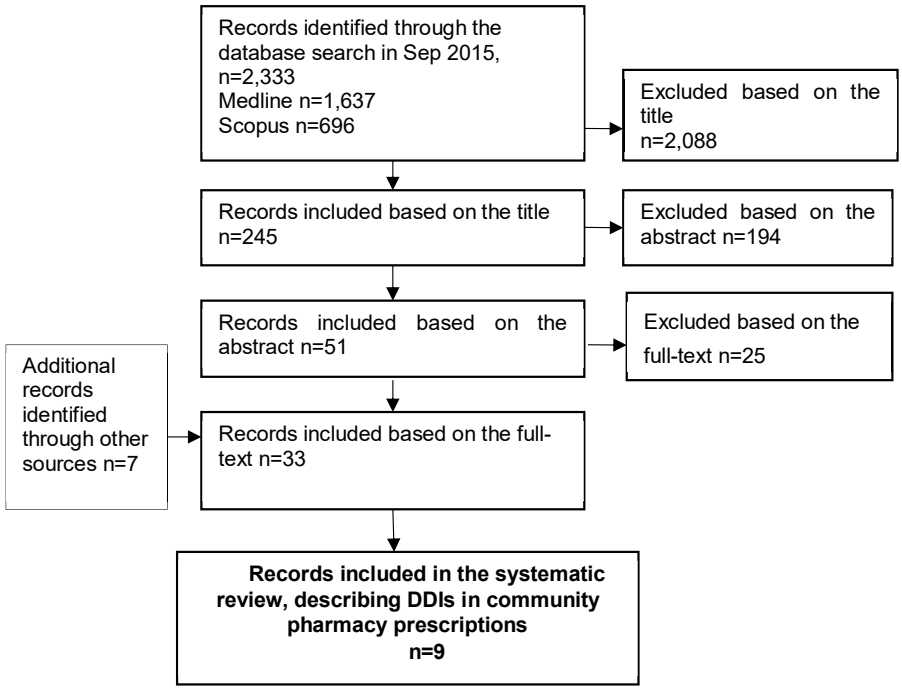


Figure 8. Selection of the included articles (n=9)

2.5.3.2 Origin of the studies, screening tools and DDI categorization used

Of the studies, two were conducted in the Netherlands (Buurma et al. 2006; Geerts et al. 2009), and one in Finland (Heikkilä et al. 2006). Other studies were from Spain, Greece, India, Romany, Germany and Iran (Cremades et al. 2009; Chatsisvili et al. 2010; Vaidhun & Sathish 2011; Bucsa et al. 2012; Nicolas et al. 2013; Dirin et al. 2014) (Table 10).

The studies (n=9) used a total of eight different methods or screening tools in DDI identification and classification. Databases used included, e.g., the FASS database (Heikkilä et al. 2006), Micromedex's Drug-Reax (Bucsa et al. 2012), Medscape database (Vaidhun and Satnish 2011), Hansten & Horn classification (Chatsisvili et al. 2011), databases from the Scientific Institute of Dutch Pharmacists (Buurma et al. 2006; Geerts et al. 2009) and from the Spanish Pharmacists Association (Cremades et al. 2009).

Table 10 Frequency and type of drug-drug interactions in the prescriptions dispensed from community pharmacies, studies (n=9) presented according to publication year

Reference	Population and data collection	Study method	DDI screening tool and classification used	Results, incidence of DDIs	Drugs with the highest number of DDIs
Buurma et al. 2006 (The Netherlands)	A total of 43,129 prescriptions dispensed from 63 Dutch community pharmacies	Each pharmacy collected all drug-drug interaction alerts during 1–3 research days. Study period 153 days in 2004.	Interactions were classified into categories of clinical relevance (A–F) and of available evidence (0–4), according to the classification of the Scientific Institute of Dutch Pharmacists	6% of all prescriptions generated a drug-drug interaction alert; percentage of prescriptions with the most serious DDIs (E and F) was 0.7%	Cardiovascular medicines (renin-angiotensin system inhibitors, beta-blockers, diuretics), NSAIDs, oral contraceptives, antibacterials
Heikkilä et al. 2006 (Finland)	39,539 prescriptions dispensed from two community pharmacies	In a prospective study, all interaction alerts given by the surveillance system were collated during a three-month study period in 2004.	Interactions were categorized into four classes (A–D) according to their clinical significance (FASS-classification)	9.8% of prescriptions (most severe Class D interactions in 0.4% and Class C interactions in 9.4% of all prescriptions)	**Class D (most severe, should be avoided)**: warfarin–NSAID; drugs interfering with absorption; ipratropium – β-receptor agonists; aldosterone antagonists – potassium; fluvoxamine – other antidepressants; **Class C (clinically significant)**: NSAID – β-adrenergic receptor antagonist; antidepressants – neuroleptics; ACE inhibitors – antidiabetic drugs
Cremades et al. 2009 (Spain)	Prescription and OTC medicines dispensed from two pharmacies in	DDIs were identified using a screening system and concerning	CGCOF-database (Spanish Pharmacists	In 1% of dispensing operations. Patient's	Calcium salts – bisphosphonates;

Reference	Population and data collection	Study method	DDI screening tool and classification used	Results, incidence of DDIs	Drugs with the highest number of DDIs
	Alicante (n=39,340 dispensing operations).	DDIs outside of the system, by community pharmacists. DDIs were screened between the drugs dispensed at same time. The study period was 6 months in 2005.	Association), not specified in detail	high age and female sex were risk factors	oral antidiabetics – thiazide diuretics; antidiabetics – glucose; oral anticoagulant – paracetamol; antidiabetic – ACE inhibitors; benzodiazepines – omeprazole
Geerts et al. 2009 (Neatherlands)	All patients from 100 Dutch community pharmacies using, according to dispensing information, two or more drugs concomitantly on a specified date (April 4, 2007) (n=223,019).	Anonymous drug-dispensing data were received through the national drug dispensing register data. For each dispensed drug the concomitant use was estimated based on the dosage and dispensed amount	A surveillance system developed and maintained by a working group of the Scientific Institute of Dutch Pharmacists. DDIs were coded using a 6-point scale for the seriousness of the potential adverse reaction (A–F) and by using a 5-point quality of evidence scale (0–4)	Of the included patients, 24.4% had one or more potential DDIs (n=54,427)	Of the most serious DDIs (Type F): agents acting on the renin-angiotensin system – potassium-sparing diuretics; tricyclic antidepressants – SSRIs/duloxetine; Potassium salts – potassium-sparing diuretics
Chatsisvili et al. 2010 (Greece)	A total of 1,553 handwritten prescriptions from three Greek community pharmacies.	Prospective, descriptive study. 3-month period (November 2007 – January 2008). DDIs were screened from the prescriptions	Drug Interaction Checker (www.drugs.com), Hansten & Horn classification: only DDIS of major or moderate significance were considered	DDI were identified in 18.5% (n=213) of all prescriptions. DDIs of major significance in 1.9% and of moderate significance in 16.6% of all prescriptions.	ACE inhibitors/angiotensin receptor antagonists + potassium-sparing diuretics; amiodarone + potassium-wasting diuretics; amiodarone + Digoxin; amiodarone + simvastatin; beta blockers + verapamil/diltiazem
Vaidhun and Sathish 2011 (India)	Prescriptions (n=500) dispensed from three community pharmacies,	All prescriptions (n=500) presented to the three pharmacies	DDIs were screened using multiple sources, e.g.,	DDIs in 12.8% of the prescriptions. Of these 10.2% were	central nervous system medications;

Reference	Population and data collection	Study method	DDI screening tool and classification used	Results, incidence of DDIs	Drugs with the highest number of DDIs
	located within a 200 meters distance.	were analyzed and the drug-drug interactions were screened.	Medscape, books, journals. Classification: Moderate, major, contraindicated	moderate, 2.6% were severe and 0% were contraindicated	diabetes mellitus medications; respiratory system medications; cardiovascular medications
Bucsa et al. 2012 (Romania)	Prescriptions dispensed from one Romanian community pharmacy: 308 prescriptions (all reimbursed prescriptions from one month) of 243 patients	In the retrospective study (January 2010), potential DDIs were screened between drugs on different prescriptions, if the drugs were meant to be taken in the same period	Micromedex (Drug-Reax) program: contraindicated, major, moderate and minor	DDIs were identified in 48.2% of patients and in 34.4% of prescriptions. Of the detected DDIs, 0% were classified as contraindicated, 19.8% as major, 76.2% as moderate and 4.0% as minor.	ACE inhibitors + thiazide diuretics; beta-adrenergic blockers + dihydropyridine; ACE inhibitors + NSAIDs; calcium channel blockers + statins; beta-adrenergic blockers + NSAIDs.
Nicolas et al. 2013 (Germany)	Prescriptions dispensed from 130 community pharmacies to 14,231 patients. Number of prescribed medicines 24,422, and prescriptions 16,767.	DDIs were screened between the prescriptions dispensed at the same time and between the medicines dispensed earlier, if the data was available.	The drug interaction database integrated into the software used in the pharmacies was developed by ABDATA (not specified).	DDIs were identified in 4.4% of all prescriptions, covering 22.9% of all detected DRPs.	Not specified.
Dirin et al. 2014 (Iran)	Community pharmacy prescriptions (n=765) and hospital pharmacy prescriptions (n=993) dispensed to outpatients	Prospective, descriptive cross-sectional study, 6-months study period, prescriptions of different community pharmacies and inpatient and outpatient pharmacies of Amir-al-Momenin teaching hospital	The prescriptions were processed using Lexi-Comp drug interaction software. The identified DDIs were categorized into five classes (A, B, C, D, X)	DDIs were identified in 34.5% of community pharmacy prescriptions and in 44.2% of hospital pharmacy outpatient prescriptions. Polypharmacy increased the risk for DDIs.	Corticosteroids + NSAIDs

2.5.3.3 Prevalence or incidence of DDIs and drugs included

The DDI prevalence rate varied markedly across the studies. The rate of identified DDIs in prescriptions varied from 4.4% (Nicolas et al. 2013) to 34.4% (Bucsa et al. 2012). The rate of DDIs classified as severe, major or contraindicated varied from 0.35% to 19.8% depending on DDI classification system and country. Drugs most frequently involved in DDIs were cardiovascular medicines, NSAIDs and antithrombotic agents (Table 11). Summary of the included studies is presented in Table 10.

Table 11 Drugs most frequently leading to a drug–drug interaction in the studies (n=9)

Drug class	Most prevalent DDIs in the drug class	Studies
Cardiovascular medicines	ACE inhibitors/angiotensin II antagonists – diuretics Beta-blocking agents – anti diabetics Potassium sparing diuretics – potassium ACE inhibitors/angiotensin receptor antagonists + potassium-sparing diuretics Verapamil – betablocker Sildenafil – nitrate	Buurma et al. 2006 Heikkilä et al. 2006 Geerts et al. 2009 Chatsisvili et al. 2010 Bucsa et al. 2012 Vaidhun and Sathish 2011
NSAIDs	NSAID – ACE inhibitors/angiotensin II antagonists/beta-blocking agents/diuretics NSAID – warfarin NSAID – methtotrexate	Buurma et al. 2006 Heikkilä et al. 2006 Bucsa et al. 2012
Antithrombotics	Warfarin – NSAID	Heikkilä et al. 2006

2.5.3.4 Recent studies (2015–2018)

An update of the literature search was conducted on October 24, 2018 using the same search strategy as in the original search. The timeframe was limited from January 1, 2015 to October 24, 2018.

Literature search produced a total of 612 articles (Medline n=473, Scopus n=139). From these, five studies met the original inclusion criteria (Table 9) (Guthrie et al. 2015; Heringa et al. 2016; Goren et al. 2017; Andersson et al. 2018; Jazbar et al. 2018). One of these studies was conducted in community pharmacy setting in the Neatherlans (Heringa et al. 2016).

Heringa et al. retrospectively analyzed drug therapy alerts generated by a CDSS in Dutch community pharmacies (Heringa et al. 2016). They investigated the frequency, nature, and determinants of drug therapy alerts generated by a CDSS in community pharmacies. The goal was to be able to propose CDSS improvement strategies for community pharmacies, aiming to reduce overridden alerts. Data was extracted from 1,672,169 prescriptions,

dispensed from a random sample of 123 community pharmacies in the period from August 2013 to July 2014. Of all prescriptions, 15% led to DDI alerts. The most common alerts involved antithrombotic agents, ACE-inhibitors and beta-blocking agents. The interactions between ACE inhibitors/angiotensin II antagonists and diuretics were the most common DDI alerts (14.8%), followed by the interactions between antidiabetics and beta-blocking agents (9.1%).

2.5.3.5 Discussion

Community pharmacies use different DDI screening tools to identify clinically significant DDIs requiring intervening action. Studies show differences between countries concerning the state of DDI screening. Most studies were conducted during the first decade of the 2000s (Table 10). The update of the literature search in 2018 yielded only one new study, aimed to develop clinical decision support systems with decreased alert rate (Hering et al. 2016).

DDI incidence estimates vary markedly across studies from different countries since the healthcare environments and systems vary. Drugs that are approved and marketed vary by country, and so do prescribing patterns. There are also big differences between drug interaction screening programs and databases regarding inclusion, severity classification and documentation levels of DDIs. Even widely used interaction screening programs differ in detecting interacting drug-drug pairs (Andersson et al. 2013; Andersson et al. 2015; Roblek et al. 2015). These differences produce markedly varying results across DDI incidence studies.

In addition to contextual differences in DDI studies, research methods used in DDI incidence studies vary. The existing studies conducted in community pharmacies were primarily focused on describing the rate of DDIs, but not service development for community pharmacists' involvement in systematic management of clinically significant DDIs in collaboration with local physicians.

2.6 SUMMARY OF THE KEY FINDINGS OF THE LITERATURE REVIEW

Patient and medication safety risks have raised the global discussion on the need for a development of health services and systems. Health services strive to provide good quality of care, but sometimes people are unintentionally harmed. Errors in patient care and related harm is a remarkable challenge in health care, influencing public health and health care costs.

A majority of medicine use takes place in primary care, where ensuring safe use is even more challenging than in hospitals since medicines are mainly taken by patients without supervision. The care has become fragmented leading to a situation where several prescribing physicians and other health professionals may participate in the care of the patient without coordinating their actions. Lack of coordination increases the risk of inappropriate medications, such as DDIs.

Cumulating worldwide evidence shows that older adults with multi-morbidities and polypharmacy are a patient group at the highest risk of medication errors and problems. Care of multi-morbid patients with polypharmacy is a growing global challenge. In addition to human suffering, medication-related adverse events cause burden to health care organizations. According to estimates, up to 11% of unexpected hospital admissions are caused by medication-related harm, 70% of them concerning multi-morbid older adults with polypharmacy (Kongkaew et al. 2013). In Finland, it is estimated that 23% of the unplanned geriatric hospital admissions result from adverse drug events (Laatikainen 2020).

The proportion of aged population ($\geq$65 years) will grow markedly during the next decades – it is estimated to grow from 11% in 2010 to 22% in 2050 (Mair et al. 2017). The importance of polypharmacy management is acknowledged globally in the WHO's third global Patient Safety Challenge "Medication Without Harm" (WHO 2017a). The trend in geriatric care is to transfer care from care homes and inpatient facilities to home care. Management of medication safety risks of these home-dwelling older patients is particularly difficult, and there is an urgent need for new strategies and practices in this respect.

Community pharmacists today already contribute remarkably to safe medication use in primary care. Finnish community pharmacies have been actively involved in patient and medication safety initiatives since the beginning of systems-based initiatives in Finland in the 2000s. They have actively developed new tools and services to improve medication safety. These include, e.g., medication counseling services (TIPPA Project 2004), automated dose dispensing, collaborative medication reviews, and DDI screening. The information technology development in community pharmacies has also aimed to support safe medication management. Even though these innovative prospective medication risk management tools and databases are widely available in Finland, they do not form an integrated medication management

process. Utilization of these tools is suboptimal unless dynamic interprofessional collaboration, including definition of roles, tasks and responsibilities is established.

A remarkable milestone towards better integration of pharmacy services in Finnish health care was the 2015 Government Program, which aimed to promote rational pharmacotherapy (Finnish Government 2015). The same Government Program also aimed to increase collaborative medication reviews in older patients. The 2018 Rational Pharmacotherapy Action Plan by the MSAH highlighted the importance of improving medication management as a whole (Ministry of Social Affairs and Health 2018). The Action Plan clearly states the need for collaborative medication reviews and pharmacists' contributions in this respect. The Action Plan goals continue to underpin the implementation-driven long-term roadmap that the MSAH produced in 2019 (Ministry of Social Affairs and Health 2019). To support the implementation, local demonstration projects are needed to find new approaches and pilot more coordinated practices, particularly to ensure the rational and safe medication use of older patients in primary care, as a part of social and health services reform.

3 AIMS OF THE STUDY

The aim of this study was to enhance prospective medication risk management in outpatient care, by enhancing coordination of care with community pharmacists' participation and use of risk management screening tools. Specific objectives of studies I-III were:

- To demonstrate how community pharmacies can utilize their prospective surveillance system for screening clinically significant DDIs in outpatients and develop a collaborative procedure with local physicians to manage clinically significant DDIs, and to assess the rate of clinically significant DDIs in a large national outpatient prescription sample (I).

- To integrate risk assessment tools, procedures and databases available in Finland in order to form a coordinated medication management model (CoMM) involving home care nurses and practical nurses (PNs), physicians and community pharmacists in the medication process of older home care clients. An RCT study design was also developed to assess the effectiveness of the intervention (II).

- To assess the impact of the care coordination intervention (CoMM) on medication risks identified in drug regimens of older home care clients over a one-year period (III).

4 MATERIALS AND METHODS

The theoretical framework of this study is systems-based risk management theory (Reason 2000) and its application to safe use of medicines. The empirical part of this thesis consists of two implementation studies in primary care (Figure 9). The Phase I study concerned implementation of the first electronic database to identify clinically significant DDIs in community pharmacies in Finland. The Phase II studies focused on 1) developing and implementing a collaborative procedure to enhance coordination in medication management between home care and community pharmacy and 2) assessing the effectiveness of the procedure (Figure 9).

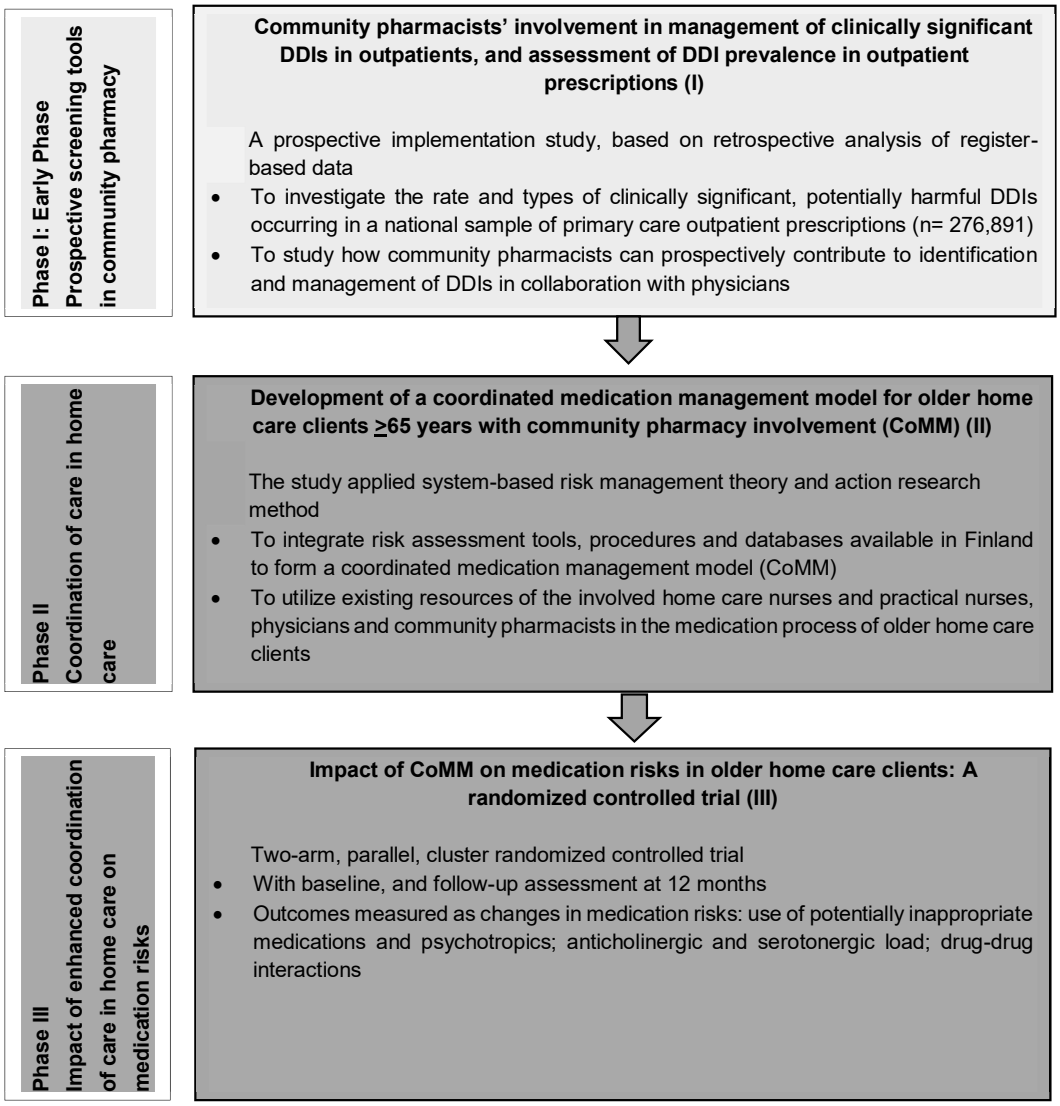


Figure 9 Outline of the study

4.1 IDENTIFYING HIGH RISK MEDICATIONS CAUSING POTENTIAL DRUG-DRUG INTERACTIONS IN OUTPATIENTS: A PRESCRIPTION DATABASE STUDY BASED ON AN ONLINE SURVEILLANCE SYSTEM (STUDY I)

4.1.1 METHODS

4.1.1.1 The DDI screening system

The prescription database study related to the implementation of the first online DDI screening system in Finnish community pharmacies. The study was conducted in the University Pharmacy, and sixteen of its seventeen outlets participated in the study.

University Pharmacy is owned by the University of Helsinki, and it is the largest community pharmacy operating in Finland dispensing about 5.8 million prescriptions per year (University Pharmacy 2018). This is about 10% of all outpatient prescriptions dispensed in Finland annually. University Pharmacy has 17 outlets in 12 large cities in different parts of the country, and the largest outlets being located in Helsinki.

University Pharmacy started to use a prospective DDI surveillance system (based on FASS) in June 2004. The surveillance system was linked to the prescription processing software (Linnea®; Receptum, Helsinki, Finland). While a prescription was processed, the surveillance system automatically screened for possible interactions in client's current and previous (in the prior 13 months) prescriptions dispensed from any of the 17 University Pharmacy outlets. Before starting this systematic, prospective interaction screening as part of the routine dispensing process, University Pharmacy trained their pharmacists and informed local physicians about this new service. The service model developed and implemented in University Pharmacy focused only on clinically significant DDIs to avoid any unnecessary work and physician consultations caused by DDI alerts that were not clinically significant.

The surveillance system was based on the FASS database (Farmaseutiska Specialiteten i Sverige), which classified DDIs according to their clinical importance (Classes A–D) and documented evidence (1–4) (Sjöqvist 1997; FASS 2003) (Table 12). The FASS database was produced by the Division of Clinical Pharmacology of the Karolinska University Hospital in Sweden (FASS 2003). The FASS classification was made by Swedish experts and was updated once a year at the time of the study. The current Inxbase (previous name SFINX) database uses the same FASS classification system (A–D), derived from the earlier Swedish interactions screening system used in this study (Böttiger et al. 2009; Andersson et al. 2015). The surveillance system recorded all potential DDIs (Classes A–D), but only clinically significant DDIs (Class D and C) were included in this study.

Table 12 The drug-drug interaction classification used in the online surveillance system in the University Pharmacy during the time of the study (FASS 2003)

CLINICAL SIGNIFICANCE
A. Probably no clinical importance.
B. Clinical importance not yet confirmed.
C. Interaction may modify the effect of the drug, but this can be controlled for example, by dose adjustment or by controlling serum level.
D. Interaction may have serious clinical consequences, for example, in form of serious adverse effects or diminished drug effect. This type of drug interaction should be avoided.
DOCUMENTED EVIDENCE
1. Incomplete case reports, in vitro studies, or a drug interaction is presumed based on the evidence coming from similar drugs.
2. At least one well documented case report.
3. Based on studies in healthy volunteers or on pilot studies in patients.
4. Based on controlled studies on relevant patient groups.

4.1.1.2 Data collection

All interaction alerts provided by the DDI surveillance system were collected during a one-month period (July 2004) at the University Pharmacy. Study data included the following information: pharmacy outlet´s name, number of all detected interactions, classification of interactions, drug names according to the Anatomical Therapeutic Chemical classification system (ATC) and dispensing dates. Patient information included only the year of birth and gender (male/female). Individual prescribers or patients could not be identified in the dataset. Thus, no ethical approval from Finnish authorities was required. The management team of University Pharmacy approved the study protocol before the study was started. The research group included two experienced clinical pharmacologists with academic PhD degrees in order to assure quality of study design, data collection, and analysis.

4.1.1.3 Data analysis

The DDI alerts were categorized into classes A, B, C and D according to the FASS database, and their frequencies and percentages were calculated. The most common interacting drug combinations in each class were analyzed. The top ten list of drugs causing potential DDIs was formed by identifying the ten drugs with the highest number of class D interaction alerts. Class C interaction alerts caused by the same drugs were also calculated.

4.2 COORDINATING RESOURCES FOR PROSPECTIVE MEDICATION RISK MANAGEMENT OF OLDER HOME CARE CLIENTS IN PRIMARY CARE: PROCEDURE DEVELOPMENT (STUDY II)

4.2.1 METHODS

This study was conducted within publicly funded primary care in Lohja, a municipality in Southern Finland with 47,000 inhabitants. Health care units involved in the study were Lohja Home Care Unit, Lohja Health Center and a private community pharmacy (Lohja 1st Pharmacy). A clinically trained researcher (TT) from the research group coordinated the development of the medication management model and the study design.

Home care clients were recruited for the study by nurses and PNs. Announcements in the local newspaper were also used. The recruitment process was carried out between September 2015 and December 2015. The inclusion criteria were: 1) ≥65 years old, home-dwelling resident; 2) receives regular home care from the city of Lohja; 3) uses at least one medicine; and 4) participates voluntarily, with a written informed consent to participate in the study given by the participant or closest proxy.

4.2.1.1 Ethics approval and consent to participate

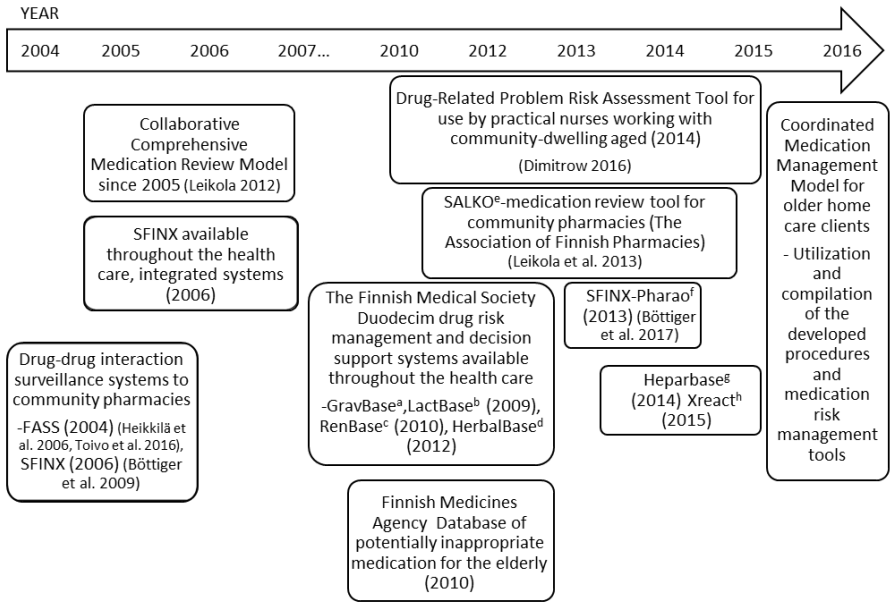
The study protocol was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS), Finland (number 153/13/03/00/15). Informed written consent was obtained from each patient and/or their closest proxy before any study procedure was performed. The study is registered in the Clinical Trials.gov (NCT02545257).

4.2.1.2 Study design

The procedure development was carried out using the action research method. The action research method is increasingly being used in health services research (Lewin 1946; Meyer 2000). When applying this method, the idea is that the researcher works with and for people rather than undertakes research on them (Meyer 2000). Reason's systems-based risk management theory (Reason 2000) and Hepler and Strand's basic principles of identifying, solving and preventing DRPs (Hepler & Strand 1990) were applied as theoretical frameworks. Clyne's model was applied for categorization of comprehensiveness of medication reviews (Clyne et al. 2008).

The goal was to construct a collaborative procedure utilizing each profession's existing resources. The coordination of the use of the risk

management tools and resources illustrated in Figure 10 was part of the process.



[a]Gravbase, [b]Lactbase: Decision support databases that give concise evidence based information on the safety of different drugs during pregnancy and lactation; [c]Renbase: Database for drug dosing in renal failure; [d]HerbalBase: Efficacy and safety of natural medicines.
(Duodecim Medical Publications Ltd.)
[e]Salko –medication review tool for 1) sedative effect; 2) anticholinergic effect; 3) serotonergic effect; 4) appropriateness for aged patients based on 4 different criteria; and 5) metabolization via 6 different CYP-enzymes.
[f]SFINX-Pharao: Drug-drug interaction database and adverse effects database: Cumulative scoring of the anticholinergicity, bleeding risk, constipation, orthostatic hypotension, prolongation of QT interval, nephrotoxicity, sedation, convulsion risk and serotonergicity of the patient's medication. (SFINX-Pharao database's new name since March 2017 is INXBASE/RISKBASE).
[g]Heparbase: Drug dosing in hepatic impairment (Duodecim Medical Publications Ltd.)
[h]Xreact: Cross-hypersensitivity between drugs (Duodecim Medical Publications Ltd.)

Figure 10 Medication risk management tools and databases launched in Finland since 2004 and currently widely available in health care and community pharmacies

4.2.1.3 Model development process

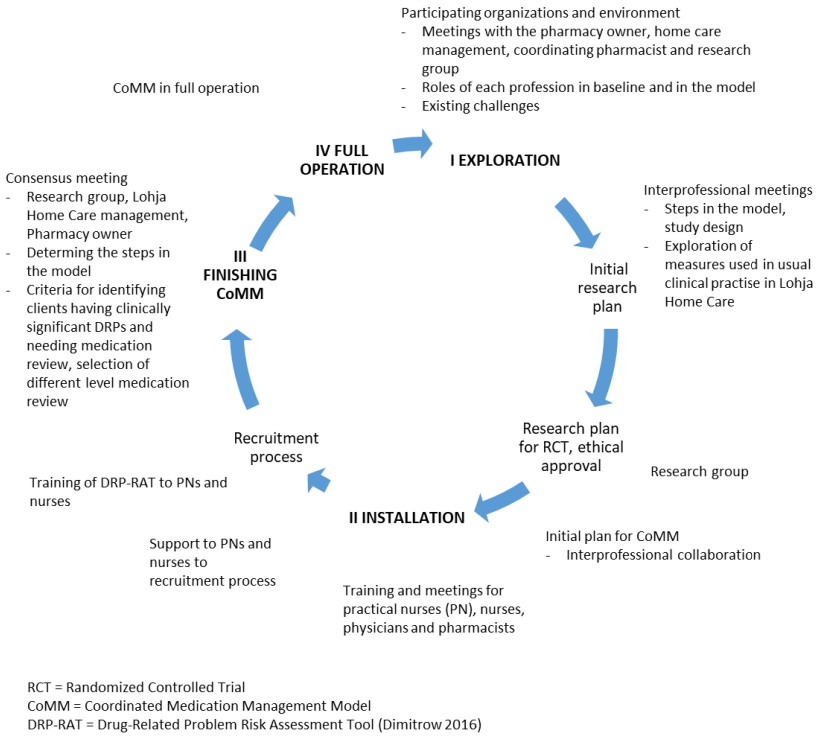
The procedure development process consisted of four main steps (Figure 11). During each step, the coordinating pharmacist/researcher (TT) worked closely with the home care nurses and PNs, their manager (nurse), physicians involved in home care and the community pharmacists.

The exploration step (Step I, Figure 11) included orientation to each organization's current medication management practices, targeted to older home care clients. It also covered identification of medication management tools and procedures applied locally in Lohja, compared to those generally

available in Finland (Figure 10). Actual tasks and responsibilities for each professional were defined in regular joint meetings with the coordinating pharmacist (TT), the pharmacy owner (ES) and the nurse responsible for the home care service area (KP).

The installation step (Step II, Figure 11) was to prepare the participating organizations for the implementation of CoMM. Home care nurses, PNs, physicians and pharmacists were informed prior to implementation of the procedure, and continuously encouraged to comment on the model construction. Personnel training sessions needed to support the model construction were jointly planned with the researchers and home care and community pharmacy management. The coordinating pharmacist organized trainings for PNs related to the recruitment process, medication reconciliation (Institute for Healthcare Improvement 2011) and use of clinical tests. PNs were also trained on the content and use of the Drug-Related Problem Risk Assessment Tool (DRP-RAT) (Dimitrow et al. 2014; Dimitrow et al. 2015) and regarding the Lohja Home Care Unit's principles in medication management (Finnish Institute for Health and Welfare 2015).

Finishing the CoMM (Step III, Figure 11) aimed to select the appropriate manner to solve the identified clinically significant DRPs and allocate medication reviews according to the severity of the DRPs. After finishing the development of CoMM, its full operation started (Step IV, Figure 11). The coordinating pharmacist worked closely with the home care practitioners and community pharmacists, facilitating integration between stages and tasks of the health care providers involved. This enabled reflection of the model's feasibility.



RCT = Randomized Controlled Trial
CoMM = Coordinated Medication Management Model
DRP-RAT = Drug-Related Problem Risk Assessment Tool (Dimitrow 2016)

Figure 11 Development process of the coordinated medication management model (CoMM) using the action research method (modified from Lewin 1946 and Meyer 2000),

4.3 IMPACT OF ENHANCED COORDINATION OF CARE ON OUTCOMES OF PROSPECTIVE MEDICATION RISK MANAGEMENT OF OLDER HOME CARE CLIENTS: A RANDOMIZED CONTROLLED TRIAL (STUDY III)

4.3.1 METHODS

This study was a clustered RCT with a one-year follow-up period. Participants were cluster randomized to intervention and control groups by home care service area (Figure 12). The study was considered as open-label. The intervention group (IG) received the intervention (CoMM) during the first year, while the control group (CG) received standard home care. After the 12-month follow-up, the CG received the same intervention.

4.3.1.1 Outcome measures and participants' characteristics

This study focused on clinically significant medication-related risks (i.e., DRPs requiring intervening actions) as primary outcomes for assessing the effectiveness of the intervention. Aspects assessed revolved around potentially inappropriate medications (PIMs), excessive use of psychotropics, anticholinergic and serotonergic load, as well as clinically significant drug-drug interactions (DDIs) (Table 13).

Participants' characteristics included demographics and the following clinical outcomes: functional ability (Rava) (Finnish Consulting Group 2019); physical performance (the five-times-sit-to-stand test) (Csuka & McCarty 1985; Guralnik et al. 1994); Mini-Mental State Examination (MMSE) (Folstein et al. 1975); Geriatric Depression Scale-15 (GDS-15) (Kurlowicz & Greenberg 2007); the Mini Nutritional Assessment (MNA) (Vellas et al. 1999); Urinary Distress Inventory (UDI-6) (Uebersax et al. 1995); Orthostatic hypotension (Short test) (Freeman et al. 2011); and Alcohol Use Disorder Identification Test, version C (AUDIT-C) (Bush et al. 1998). All clinical measures used in this study were administered by the PNs and nurses during a separate home visit. Majority of the applied outcome measures were already part of normal clinical use in Lohja Home Care.

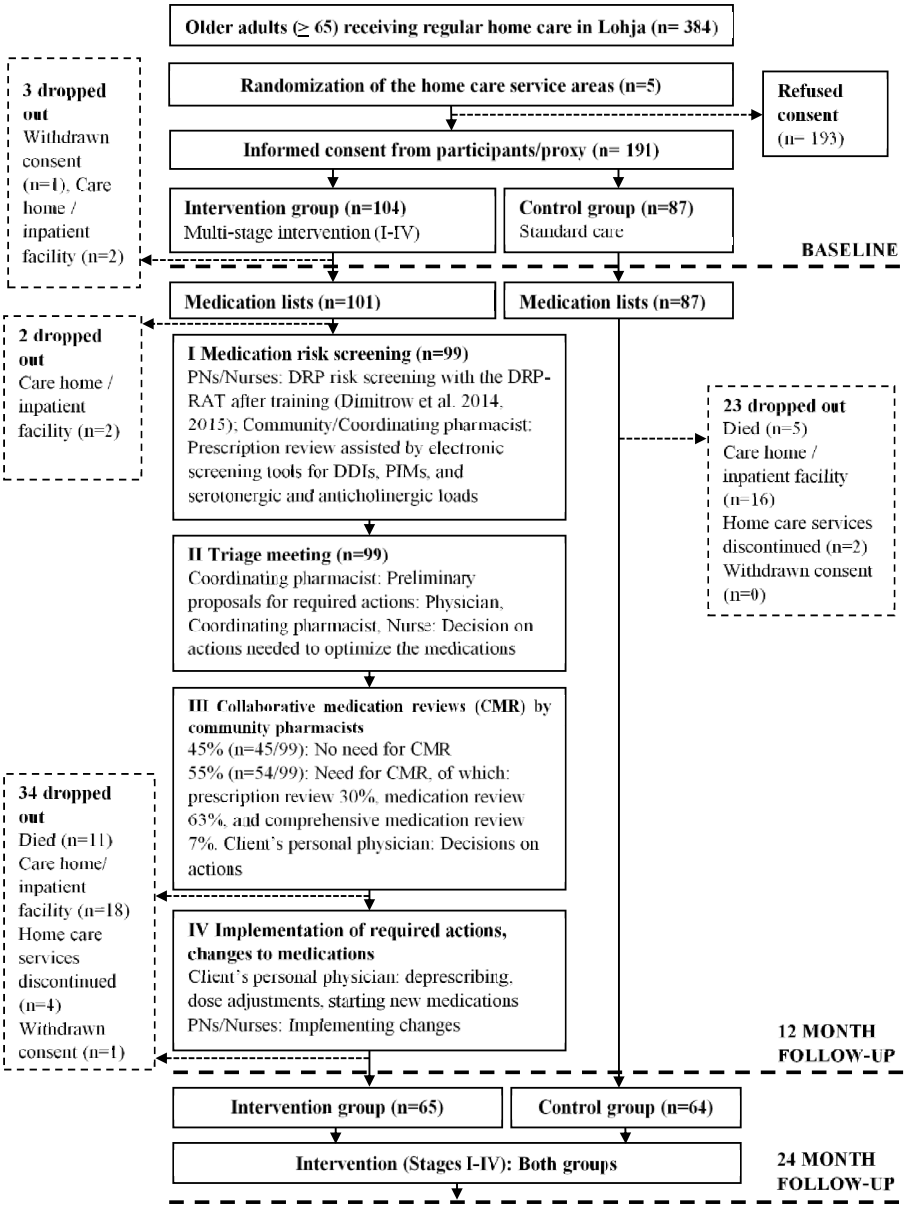


Figure 12 Study flow chart

Table 13 Clinically significant medication-related risks that were assessed as outcomes in this study

Outcome	Aspects assessed
Medication-related outcomes	
Number of all medications	The total number of regular and pro re nata (when required) medications that have been prescribed (i.e., prescribed medication that is scheduled), over-the-counter and herbal products are not included
Use of harmful medications	Included Beers Criteria medications (American Geriatrics Society 2015), psychotropic and anticholinergic medications according to Puustinen et al. (2012)
Use of Beers Criteria medications (American Geriatrics Society 2015)	Potentially inappropriate medicines for older adults according to Beers Criteria (American Geriatrics Society 2015)
Use of central nervous system (CNS) medications	Opioids (ATC code N01AH, N02A, N02BE51, R05DA, R05FA); anticholinergic drugs according to Puustinen et al. (2012), antiepileptics (ATC code N03A); BZDs and related drugs (ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71); antidepressants (ATC codes N06A, N06CA); antipsychotics (ATC codes N05A, N06CA01)
Use of psychotropic medications Proportion of study participants using ≥3 psychotropic medications, n (%)	BZDs and related drugs (ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71); antidepressants (ATC codes N06A, N06CA); antipsychotics (ATC codes N05A, N06CA01) (Puustinen et al. 2012)
Proportion of study participants using ≥2 serotonergic medications, n (%)	Serotonergic medications according to Salko database (Leikola et al. 2013)
Proportion of study participants using anticholinergic medications	Anticholinergic medicines according to Puustinen et al. (2012)
Proportion of study participants using antipsychotics, n (%)	ATC codes N05A, N06CA01
Proportion of benzodiazepine (BZD) users, n (%)	BZDs and related drugs (ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71) (Puustinen et al. 2012)
Proportion of opioid users, n (%)	ATC codes N01AH, N02A, N02BE51, R05DA, R05FA
Proportion of proton-pump inhibitor (PPI) users, n (%)	ATC A02BC
Prevalence of clinically significant drug-drug interactions (SFINX class D) (Böttiger et al. 2009)	Interactions that should be avoided or used with caution (Böttiger et al. 2009)

4.3.2 STATISTICAL ANALYSES

Reconciled medication lists gathered from both intervention and standard care group participants at baseline and at the 12-month follow-up point were analyzed for medication-related risks. All participants who were assessed at baseline and at 12-month follow-up were included in the analyses. Since medication changes proposed in the medication reviews were only partly implemented, data was analyzed with the intention to treat (ITT) and per protocol analysis.

4.3.2.1 Baseline analyses

Baseline analyses were conducted to compare the participants' characteristics and the clinically significant medication risks between the IG and CG participants. Participants' characteristics included demographics and the following clinical outcomes: functional ability (Rava) (Finnish Consulting Group 2019); physical performance (the five-times-sit-to-stand test) (Csuka & McCarty 1985; Guralnik et al. 1994); Mini-Mental State Examination (MMSE) (Folstein et al. 1975); Geriatric Depression Scale-15 (GDS-15) (Kurlowicz & Greenberg 2007); The Mini Nutritional Assessment (MNA) (Vellas et al. 1999); Urinary Distress Inventory (UDI-6) (Uebersax et al. 1995); Orthostatic hypotension (Short test) (Freeman et al. 2011); and Alcohol Use Disorder Identification Test, version C (AUDIT-C) (Bush et al. 1998).

Analyses were performed using a two-sample t-test for normally distributed variables and by Mann-Whitney U-test for non-normally distributed variables. Chi-square or Fisher's exact test was used for categorical variables.

4.3.2.2 Intention to treat- and per protocol analyses

For the ITT analysis all the participants were included in the group in which they belonged to (IG or CG) regardless of whether medication changes agreed on were implemented. Per protocol analysis included only those IG participants who had at least one of the medication changes actually implemented during the follow-up.

Descriptive statistics (mean, median, or percentages as appropriate) were used to present the participant characteristics. The changes within and between groups in continuous variables were analyzed with repeated measures analysis of variance. Dichotomous outcomes were analyzed through binary logistic regression using generalized estimating equations to account for the correlation between the repeated measurements. Results are expressed using odds ratios (OR) with 95% confidence intervals (CI). ITT analyses were adjusted for functional ability and the use of antiepileptic medications, and per protocol analyses were adjusted for functional ability (Rava), use of central nervous system medications (CNS-medications), GDS-15 and MNA due to

group differences at baseline. The longitudinal analysis included participants with baseline measurement and at least one follow-up measurement at the 12-month follow-up point. Two-sided statistical tests with a 5% level of significance were used.

5 RESULTS

5.1 IDENTIFYING HIGH RISK MEDICATIONS CAUSING POTENTIAL DRUG-DRUG INTERACTIONS IN OUTPATIENTS: A PRESCRIPTION DATABASE STUDY BASED ON AN ONLINE SURVEILLANCE SYSTEM (STUDY I)

5.1.1 RATE OF POTENTIAL DDIS IN PRESCRIPTIONS

Potential drug–drug interactions were studied using 276,891 dispensed prescriptions. Potential DDIs were associated with 11.2% of all prescriptions (Table 14). Clinically significant interactions belonging to FASS class D (most severe, should be avoided) and C (clinically significant but controllable) were associated with 0.5% and 7.2% of prescriptions, respectively.

Table 14 Potential drug-drug interactions in the study material (n=276,891 outpatient prescriptions) according to their clinical significance (FASS 2003)

Code and clinical significance of interaction		n	Percentage of all interactions, %	Interaction rate in prescriptions, %
D	Most severe, interaction that should be avoided	1,512	4.8	0.5
C	Interaction may modify the effect of the drug, controllable, e.g., by dose adjustment	20,026	64.4	7.2[1]
B	Clinical importance not yet confirmed	8,824	28.4	3.2[2]
A	Probably no clinical importance	748	2.4	0.3
	Total	31,110	100.0	11.2[3]

[1]The value presented in the publication (Toivo et al. 2016) is 7.0, the difference is due to rounding of numerical values; [2]The value presented in the publication (Toivo et al. 2016) is 3.0, the difference is due to rounding of numerical values; [3]The value presented in the publication (Toivo et al. 2016) is 10.8, the difference is due to rounding of numerical values

5.1.2 MOST FREQUENT CLINICALLY SIGNIFICANT INTERACTION ALERTS AND DRUGS INVOLVED

The most frequent class D (most severe, should be avoided) interactions were methotrexate combined with NSAIDs (n=549), warfarin combined with NSAIDs (n=404), fluoroquinolones combined with cations (e.g. iron, calcium) (n=91) and spironolactone/amiloride combined with potassium (n=66) (Table 15).

Potential drug–drug interactions belonging to class C were the most common interactions in this study. Class C DDIs accounted for 64.4% of all detected DDIs (n = 20,026), the rate in prescriptions being 7.2%. They most commonly concerned interactions between antihypertensive drugs and NSAIDs (35.3% of all class C interactions, n=7,066) and interactions between psychotropic drugs. Interactions involving antidepressants accounted for 20.2% of class C interaction alerts (n=4,044). DDIs of antidepressants were most commonly between antipsychotics (11.5%, n=2,312) and between other antidepressants, of which venlafaxine, fluoxetine and paroxetine were most common (5.0%, n=995).

Table 15 The most common potentially serious drug-drug interactions and their percentage of all class D interaction alerts (n=1,512) and the nature of the interaction. Study material: 276,891 dispensed outpatient prescriptions

Drug(s)	Drug(s)	% (n)	Nature of interaction (FASS 2003)
Methotrexate	NSAIDs[1]	36.3 (549)	NSAIDs may reduce the tubular clearance of methotrexate
Warfarin	NSAIDs[1]	26.7 (404)	Risk for gastrointestinal bleeding
Fluoroquinolones	Calcium/iron	6.0 (91)	Inhibition of the absorption of fluoroquinolones
Spironolactone/ amiloride	Potassium	4.4 (66)	Risk for hyperpotassemia
Verapamil	ß-adrenoceptor blockers	2.6 (39)	Risk for bradycardia
Sildenafil	Organic nitrate	3.0 (46)	Risk for severe hypotension, ischemia and damage in brain and hearth

5.2 COORDINATING RESOURCES FOR PROSPECTIVE MEDICATION RISK MANAGEMENT OF OLDER HOME CARE CLIENTS IN PRIMARY CARE: PROCEDURE DEVELOPMENT (STUDY II)

5.2.1 CARE COORDINATION MODEL FOR HOME CARE CLIENTS (COMM)

The developed coordinated medication management model (CoMM) consists of five main stages in which clinically significant DRPs can be identified and solved using collaborative procedures and medication reviews (Figure 13). PNs were trained to observe potential medication risks on routine home visits more systematically than before and to report detected clinically significant DRPs to the coordinating pharmacist (Figure 13: Stage I: Risk Assessment). The coordinating pharmacist prepared the cases for the triage meeting (Figure 13: Stages I and II), in which the leading home care physician and the coordinating pharmacist decided on further action for clients with clinically significant DRPs (50–70 cases per triage meeting of two hours). The actions included more comprehensive medication reviews according to the needs of the clients, involving their own physicians and nurses/PNs. In the most complicated cases home visits were undertaken and the client's clinical interview was conducted (Figure 13: Stage III).

After the collaborative medication reviews, each client's physician made the final decisions regarding the changes to the medication regimens (Figure 13, Stage IV). In some cases, the physician wanted to meet the home care client and discuss the changes. In most cases, home care nurses who knew the clients discussed the changes with them and implemented the changes according to the physician's orders. This was a normal routine in the home care context of Finland, due to the limited physician resources. At the follow-up stage (Figure 13, Stage V), PNs and nurses monitored clients' condition, particularly when medication changes were implemented. Collaborative tasks of each healthcare professional in the developed model (Figure 13) are described in Table 16. Nurses and PNs had a key role in clinical follow-up and identifying clients with clinically significant DRPs, through gathering and bringing information about clients' symptoms and signs using the DRP-RAT.

Community pharmacists' pharmacotherapeutic skills were utilized in medication reviews at Stage III (Figure 13). Physicians' resources were allocated for clinical decision-making at the triage stage (Stage II) and for deciding on actions for clients with complicated DRPs, analyzed in more detail in the prescription review (PR), medication review (MR) or comprehensive medication review (CMR) (Stage IV). The coordinating pharmacist had a key role in organizing and coordinating medication management processes between the fragmented organizations involving different health care providers, and in preparing and participating in the triage meetings followed by different level medication reviews.

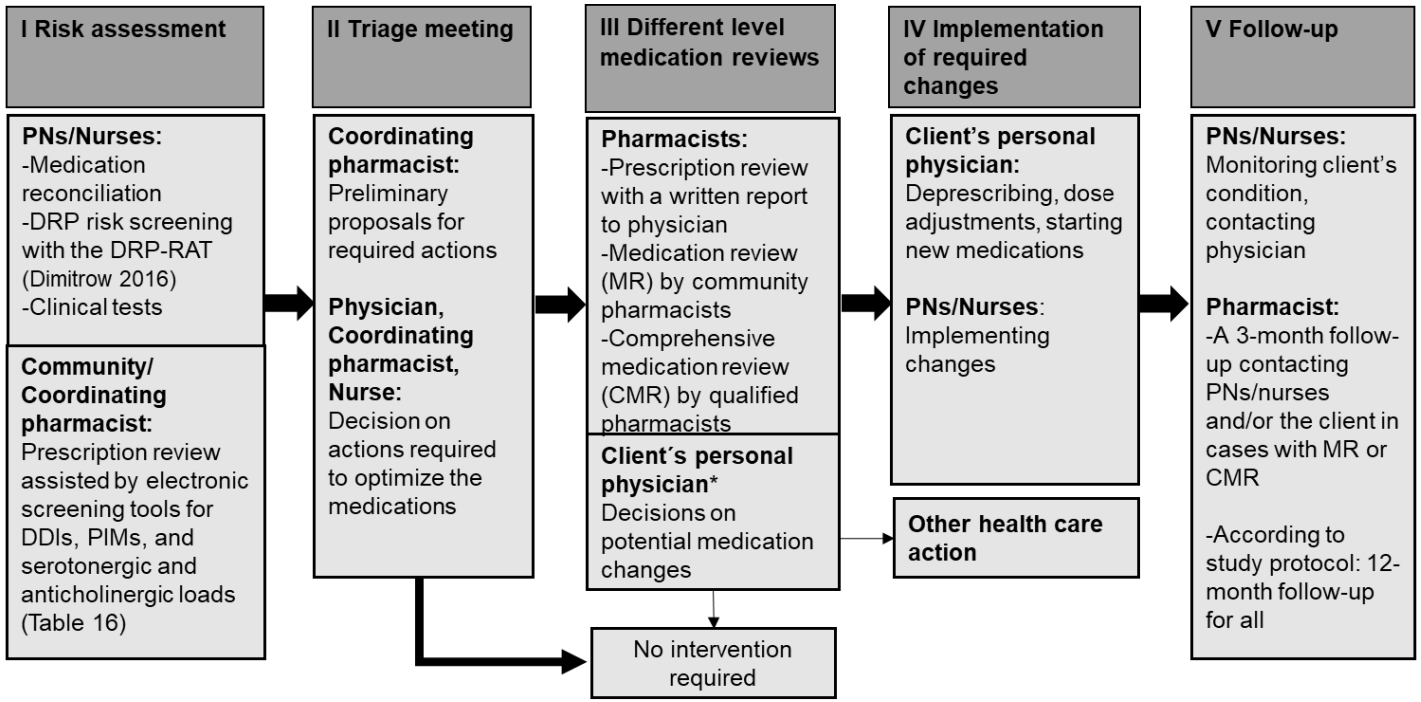


Figure 13 Triage process within the developed coordinated medication management model (CoMM) for older home clients

Table 16 Agreed tasks of each healthcare professional and tools used in the coordinated medication management model (CoMM)

Healthcare professionals	Tasks in the coordinated medication management model	Tools used
Home care nurses, practical nurses	Medication reconciliation Medication risk assessments Clinical tests to assess clients' functional ability and disability (at baseline, follow-ups at 12 and 24 months)	Medication lists, usual home visits Clinical interviews with the DRP-RAT a) Measures used in usual clinical practice: functional ability (RAVA), physical performance (the five-times-sit-to-stand test), cognitive functioning (MMSE), depression (GDS-15) and malnutrition (MNA) b) Added measures: difficulties related to urination (UDI-6), orthostatic hypotension (3 minutes test) and alcohol use (AUDIT-C)
	Implementing medication changes and monitoring their outcomes	Regular home visits as usual Informing physicians when needed
Community pharmacists	Prescription review (PR)	Clinically significant drug-drug interactions (DDIs) (SFINX). Potentially inappropriate medicines (PIMs) according to Beers 2015 criteria (AGS 2015), anticholinergic and serotonergic loads of medicines (Salko)
	Medication review (MR)	Patient information: medication list, DRP-RAT and glomerulus filtration rate (GFR) results Screening tools used: SFINX (DDIs); Pharao (Cumulative scoring of the anticholinergicity, bleeding risk, constipation, orthostatic hypotension, prolongation of QT interval, nephrotoxicity, sedation, convulsion risk and serotonergicity of the patient's medication); Salko (PIMs); Renbase (Renal function and appropriateness of doses/medicines used)
	Comprehensive medication review (CMR) conducted by a qualified pharmacist (TT,SL)	Patient information: medication list, DRP-RAT and GFR results, diagnosis, laboratory test results Tools used: As in MR, complemented by client's clinical interview
Coordinating pharmacist	Trainings of the PNs for the recruitment process, CoMM and use of DRP-RAT (MD)	Meetings, discussions, personal guidance, DRP-RAT training (Dimitrow et al. 2015)
	Coordinating and organizing processes for CoMM	Constructing the CoMM structure through observations, meetings, contacts and negotiations with organizations, health care professionals, researchers and home care clients involved, organizing processes and interactive training, providing training, guidance and feedback, reflecting the literature and guidelines on geriatric care and pharmacotherapy
	Preparing triage meetings with the leading home care physician to decide on actions for clients with clinically significant DRPs	Prescription review findings (from SFINX and Salko databases) and DRP-RAT results
Leading home care physician	Triage meetings with the coordinating pharmacist and nurse to decide on actions for clients with clinically significant DRPs (50-70 cases per triage meeting of 2 hours)	Prescription review findings (from SFINX and Salko databases) and DRP-RAT results
Client's personal physician	Case-conferences with pharmacists concerning clients with clinically	Medication lists accomplished with the SFINX and Salko data, DRP-RAT results, results from the clinical and laboratory test (GFR)

	significant DRPs identified in MR and CMR. Decisions on the medication changes and how they will be implemented	Reports with clinically significant findings from prescription review, MR and CMR (CMR report including client's clinical interview)

Abbreviations: DRP-RAT, Drug-Related Problem Risk Assessment Tool (Dimitrow 2016); MMSE, Mini Mental State Examination (Folstein et al. 1975); GDS-15, Geriatric Depression Scale (Kurlowicz et al. 2007); MNA, The Mini Nutritional Assessment (Vellas et al.1999); UDI-6 (Urinary Distress Inventory) (Uebersax et al. 1995); AUDIT-C (Alcohol Use Disorder Identification Test, version C) (Bush et al. 1998); SFINX: Drug-drug interaction database's new name since March 2017 is INXBASE; Pharao: adverse effects database's new name since March 2017 is RISKBASE.

5.3 IMPACT OF ENHANCED COORDINATION OF CARE ON OUTCOMES OF PROSPECTIVE MEDICATION RISK MANAGEMENT OF OLDER HOME CARE CLIENTS: A RANDOMIZED CONTROLLED TRIAL (STUDY III)

5.3.1 STUDY PARTICIPANTS

Of 384 eligible home care clients, 191 (49.7%) clients or their proxies provided written consent to participate (Figure 12). The intervention group (IG) included 104 participants, of which three dropped out before baseline data gathering. The control group (CG) included 87 study participants. There was a remarkable attrition rate, with 59 participants (31.4%) lost to follow-up at 12 months. In the IG, attrition rate was 35.6% (n=36) and in the CG 26.4% (n=23) (p=0.18) (Figure 12). Drop-out analysis between the IG and CG participants did not show statistically significant differences in baseline characteristics (data not shown). The number of participants with baseline and 12-month follow-up data available, included into the analyses, was 129.

The mean age of the participants (n=129) was 82.8 years (SD 7.05), 82.5% (n=104) were living alone and 69.8% (n=90) were women (Table 17). The mean number of prescription medications (regular and pro re nata, i.e., when required) was 13.5 (SD 3.87) in the IG compared with 12.7 (SD 4.30) in the CG (p=0.25).

5.3.2 USE OF PIMS AT BASELINE

Use of PIMs, excessive use of psychotropics and high anticholinergic and serotonergic load was common in both groups at baseline (Table 18). Prevalence of Beers Criteria (American Geriatrics Society 2015) medication use was 93.9% in IG and 90.6% in CG (p=0.53*)*; anticholinergic use was 27.7% in IG and 18.8% in CG (p=0.23); and ≥3 psychotropics use was 20.0% in IG and 9.4% in CG (p=0.09) (Table 18). The most commonly used Beers Criteria medications were proton pump inhibitors (PPIs), when used for longer than two months without precise indication: this was the case for 50.4% (n=60) of the Beers Criteria medication users (n=119).

Table 17 Baseline characteristics of participants (including all participants assessed at baseline and at 12-month follow-up)

	N	Total	Intervention Group (n=65)	Control Group (n=64)	p^c
Female, n (%)	129	90 (69.8)	44 (67.7)	46 (71.9)	0.61
Mean age; years, (SD), range	129	82.8 (7.1), 65–96	81.6 (7.1), 65–95	84.0 (6.8),67–96	0.05
Age group, n (%)	129				0.08
65–69		8 (6.2)	5 (7.7)	3 (4.7)	
70–74		9 (7.0)	5 (7.7)	4 (6.3)	
75–79		17 (13.2)	13 (20.0)	4 (6.3)	
80–84		41 (31.8)	21 (32.3)	20 (31.3)	
85+-		54 (41.9)	21 (32.3)	33 (51.6)	
Living alone, n (%)	126	104 (80.6)	53 (84.1)	51 (81.0)	0.64
Rava index[a,b], mean (SD)	128	1.98 (0.61)	2.19 (0.63)	1.77 (0.51)	<0.001
MD		1.83	2.08	1.59	
MNA Screening[b]	127				0.14
Normal nutritional status (12–14 points), n (%)		65 (51.2)	30 (46.9)	35 (55.6)	
At risk of malnutrition (8–11 points), n (%)		54 (42.5)	32 (50.0)	22 (34.9)	
Malnourished (0–7 points), n (%)		8 (6.3)	2 (3.1)	6 (9.5)	
MMSE[b]	126				0.44
25–30 (no cognitive impairment), n (%)		44 (34.9)	19 (30.7)	25 (39.1)	
18–24 (mild cognitive impairment), n (%)		70 (55.6)	38 (61.3)	32 (50.0)	
0–17 (moderate to severe cognitive impairment), n (%)		12 (9.5)	5 (8.1)	7 (10.9)	
GDS-15[b] ≥6 (suggestive of depression), n (%)	127	39 (30.7)	21 (33.3)	18 (28.1)	0.52
Proportion with orthostatic hypotension, n (%)	106	24 (22.6)	14 (29.2)	10 (17.2)	0.14
UDI-6 , mean (SD)	126	3.2 (4.0)	3.26 (4.4)	3.2 (3.6)	0.92
MD		2.0	2.0	2.0	
AUDIT-C , mean (SD)	128	0.9 (1.7)	1.2 (1.9) 0.0	0.72 (1.5)	0.59
MD		0.0	0.0	0.0	
The five-times-sit-to-stand test[b].	128				
Participants with inability to complete the test, n (%)		52 (40.6)	32 (50.0)	20 (31.3)	0.03
Medication use	129				
Number of regular medications, mean (SD)		10.1 (3.3)	10.4 (3.3)	9.8 (3.2)	0.25
Number of pro re nata medications, mean (SD)		3.0 (1.8)	3.1 (1.7)	2.9 (1.8)	0.54
Number of all medications, mean (SD)		13.1 (4.1)	13.5 (3.9)	12.7 (4.3)	0.25
Number of all medication, classified					0.53
1–6, n (%)		5 (3.9)	1 (1.5)	4 (6.3)	
7–9, n (%)		16 (12.4)	7 (10.8)	9 (14.1)	
10–15, n (%)		76 (58.9)	40 (61.5)	36 (56.3)	
16+, n (%)		32 (24.8)	17 (26.2)	15 (23.4)	

SD: standard deviation; MD: median; MNA: the Mini Nutritional Assessment (Vellas et al. 1999); MMSE: Mini-Mental State Examination) (Folstein et al. 1975); GDS-15: Geriatric Depression Scale (Kurlowicz and Greenberg 2007); UDI-6: Urinary Distress Inventory (Uebersax et al. 1995); AUDIT-C: Alcohol Use Disorder Identification Test, version C (Bush et al. 1998); the five-times-sit-to-stand test (Csukat et al. 1985; Guralnik et al. 1994); [a]Rava index (FCG 2019), describes the need of help based on functional ability (scale 1.29–4.03; results 1.50–1.99 mean need for regular help); [b]measure used in usual clinical practice in Lohja Home Care; [c]differences between the groups were tested with Chi-squared test or Fischer exact test in categorical variables and with Mann-Whitney test or two-sample t-test in continuous variables

5.3.3 EFFECT OF THE INTERVENTION ON THE USE OF PIMs (ITT ANALYSES)

No clinically significant medication-related risks requiring collaborative medication review were found for 45.5% (n=45) of the 99 IG participants who had DRP-RAT assessment available (Figure 12). Of the remaining 54.5% (n=54), prescription review was needed in 29.6% (n=16), medication review in 63.0% (n=34), and comprehensive medication review in 7.4% (n=4) of the cases.

The mean number of all medications in use increased in both groups over the 12-month follow-up period: in IG from 13.5 to 14.1 (adjusted mean change 0.77 95% CI 0.05–1.48; p=0.04) and in CG from 12.7 to 13.0 (adjusted mean change 0.52 95% CI -0.37–1.41; p= 0.25) (Table 18). The prevalence of PIM use remained mainly constant in both groups. No significant changes ($p \leq 0.05$) were found in any selected medication-related outcomes between the IG and CG in the ITT analyses (Table 18).

5.3.4 PER PROTOCOL ANALYSES

Per protocol analysis compared IG participants with at least one implemented medication change (n=27) with CG participants (n=64) (Table 19). No significant differences ($p \leq 0.05$) were found in medication-related outcomes between the IG per protocol (IG_{pp}) and CG over the 12-month follow-up period (Table 19). However, a tendency for a decrease was found in the use of central nervous system (CNS) medications between the groups (p=0.08): in IG_{pp} a decrease of 18.5% was observed (adjusted OR 0.15 95% CI 0.03–0.80), compared to a decrease of 3.1% (adjusted OR 0.81 95% CI 0.37–1.77) in CG.

5.3.4.1 Analyses within the per protocol group (n=27)

In the analyses within the IG_{pp}, in addition to a decrease in CNS use (from 92.6% to 74.1%; adjusted OR 0.15, 95% CI 0.03–0.80; p=0.03), the use of benzodiazepines (BZDs) decreased from 55.6% to 37.0% (adjusted OR 0.43, 95% CI 0.21–0.91; p=0.03). A tendency for a decrease within the IG_{pp} ($p<0.10$) was shown in the following outcomes: proportion of persons using ≥ 3 psychotropic medications decreased from 18.5% to 7.4% (p=0.07) and opioid use decreased from 40.7% to 26.0% (p=0.09) (Table 19).

Table 18 Outcomes describing potentially inappropriate medicine use at baseline and after 12 months in the intervention and control groups and significance of changes within and between the groups during the follow-up

Medication in use	Intervention group (N=65)				Control group (N=64)				
	Baseline	At 12 months	Adjusted mean change [95% CI] or adjusted OR (95% CI) for change	p for change	Baseline	At 12 months	Adjusted mean change [95% CI] or adjusted OR (95% CI) for change	p for change	P[h] for the difference in change between the groups
Number of all medications, mean (SD)	13.5 (3.9)	14.1 (3.8)	0.77 [0.05–1.48]	0.04	12.7 (4.30)	12.95 (4.03)	0.52 [-0.37 - 1.41]	0.25	0.59
Harmful medication[a] user, n (%)	56 (86.2)	57 (87.7)	1.15 (0.63 - 2.10)	0.66	51 (79.7)	51 (79.7)	1.00 (0.63 - 1.60)	1.00	0.73
Beers Criteria (AGS 2015) medication user, n (%)	61 (93.9)	63 (96.9)	2.12 (0.34 - 13.2)	0.42	58 (90.6)	57 (89.1)	0.84 (0.39 - 1.82)	0.66	0.36
Psychotropic medication[b] user, n (%)	43 (66.2)	45 (69.2)	1.15 (0.78 -1.72)	0.48	32 (50.0)	30 (46.9)	0.88 (0.62 - 1.25)	0.48	0.32
Anticholinergic medication[c] user, n (%)	18 (27.7)	17 (26.2)	0.92 (0.58 - 1.42)	0.74	12 (18.8)	12 (18.8)	1.00 (0.75 - 1.33)	1.00	0.77
CNS medication[d] user, n (%)	56 (86.2)	53 (81.5)	0.69 (0.34 - 1.41)	0.31	45 (70.3)	43 (67.2)	0.86 (0.49 - 1.50)	0.59	0.64
Therapeutic duplication									
Proportion using ≥3 psychotropic medications[b], n (%)	13 (20.0)	12 (18.5)	0.81 (0.53 - 1.22)	0.31	6 (9.4)	5 (7.8)	0.82 (0.41 - 1.62)	0.57	0.97
Proportion using ≥2 serotonergic medications, n (%)	13 (20.0)	16 (24.6)	1.35 (0.88 - 2.06)	0.17	5 (7.8)	7 (10.9)	1.47 (0.69 - 3.16)	0.32	0.84
Use of special ATC classes									
Antipsychotics users[e], n (%)	13 (20.0)	15 (23.1)	1.20 (0.72- 2.01)	0.48	7 (10.9)	7 (10.9)	1.00 (0.64 - 1.57)	1.00	0.59
BZD[f] users, n (%)	32 (49.2)	30 (46.2)	0.88 (0.62 - 1.25)	0.48	21 (32.8)	20 (31.3)	0.93 (0.64 - 1.35)	0.70	0.83
Opioid[g] users, n (%)	18 (27.7)	17 (26.2)	0.92 (0.55 - 1.55)	0.76	22 (34.4)	20 (31.3)	0.87 (0.58 - 1.29)	0.48	0.85
PPI (ATC A02BC) user, n (%)	30 (46.2)	30 (46.2)	1.00 (0.78 - 1.29)	1.00	30 (46.9)	33 (51.6)	1.21 (0.92 - 1.59)	0.17	0.31
Drug-drug interactions (DDI)									
Clinically significant DDI (class D)(Böttiger et al.2009), n (%)	7 (10.8)	6 (9.2)	0.84 (0.39 - 1.79)	0.65	1 (1.6)	0 (0)	NA	0.32[i]	NA

SD=standard deviation; OR=odds ratio; CI = confidence interval; CNS = central nervous system; BZD = benzodiazepine; PPI = proton-pump inhibitor medicine

[a] **Harmful medications** included **1) Beers Criteria medications (AGS 2015), 2) [b] psychotropic medications** (included [f]*BZDs and related drugs*: ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71; a*ntidepressants*: ATC codes N06A, N06CA; [e]*antipsychotics*: ATC codes N05A, N06CA01); **3) [c] anticholinergic** medications: ATC codes: N04A, N05AA01, N05AA02, N05AB01, N05AB02, N05AB03, N05AB04, N05AC01, N05AC02, N05AF01, N05AF03, N05AF05, N05BB01, N06AA04, N06AA06, N06AA09, N06AA12, N02AG, A03AA, A03AB, A03AX03, A03B, A03CA, A03CB31, A03DA, A03FA01, A04AD01, A04AD12, C01BA01, C01BA03, C01BA51, C01BA71, R03BB, M03B, G04BD, S01FA, R01BA01, R01BA51, R06AB01, R06AE03, R06AE53). If the medication appeared in two or more criteria, they were considered only once.
[d]**CNS medications**: [g]opioids (ATC codes: N01AH, N02A, N02BE51, R05DA, R05FA), [c]anticholinergics; antiepileptics (ATC N03A); [f]BZDs and related drugs (ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71); Antidepressants (ATC codes N06A, N06CA); [e]Antipsychotics (ATC codes N05A, N06CA01).
[h]Adjusted for functional ability Rava and the use of antiepileptic medications (ATC code N03A).[i] McNemar test due to zero frequencies.

Table 19 Outcomes describing potentially inappropriate medicine use at baseline and after 12 months in the *per protocol* intervention group and control groups and significance of changes within and between the groups during the follow-up

Medication in use	Intervention group (N=27)				Control group (N=64)				
	Baseline	At 12 months	Adjusted mean change [95% CI] or adjusted OR (95% CI) for change	p for change	Baseline	At 12 months	Adjusted mean change [95% CI] or adjusted OR (95% CI) for change	p for change	P[i] for the difference in change between the groups
Number of all medications, mean (SD)	14.0 (3.9)	13.3 (3.3)	-0.02 [-1.24 -1.20]	0.97	12.7 (4.3)	13.0 (4.0)	0.38 [-0.59-1.36]	0.44	0.46
Harmful medication[a] user, n (%)	23 (85.2)	22 (81.5)	0.61 (0.13 - 2.88)	0.54	51 (79.7)	51 (79.7)	1.00 (0.50 - 2.02)	1.00	0.58
Beers Criteria (AGS 2015) medication user, n (%)	26 (96.3)	25 (92.6)	0.42 (0.02 - 7.52)	0.56	58 (90.6)	57 (89.1)	0.82 (0.34 - 1.95)	0.65	0.67
Psychotropic medication[b] user, n (%)	21 (77.8)	19 (70.4)	0.47 (0.04 - 5.24)	0.54	32 (50.0)	30 (46.9)	0.56 (0.11 - 2.72)	0.47	0.90
Anticholinergic medication[c] user, n (%)	8 (29.6)	5 (18.5)	0.62 (0.25 - 1.56)	0.31	12 (18.8)	12 (18.8)	1.00 (0.72 - 1.39)	1.00	0.34
CNS medication[d] user, n (%)	25 (92.6)	20 (74.1)	0.15 (0.03 - 0.80)	0.03	45 (70.3)	43 (67.2)	0.81 (0.37 - 1.77)	0.59	0.08
Therapeutic duplication									
Proportion using ≥ 3 psychotropic medications[b], n (%)	5 (18.5)	2 (7.4)	0.35 (0.11 - 1.10)	0.07	6 (9.4)	5 (7.8)	0.82 (0.42 - 1.62)	0.56	0.21
Proportion using ≥ 2 serotonergic medications, n (%)	6 (22.2)	7 (26.0)	1.28 (0.56 - 2.92)	0.56	5 (7.8)	7 (10.9)	1.49 (0.68 - 3.26)	0.32	0.79
Use of special ATC classes									
Antipsychotics users[e], n (%)	6 (22.2)	4 (14.8)	0.59 (0.20 - 1.69)	0.32	7 (10.9)	7 (10.9)	1.00 (0.61 - 1.65)	1.00	0.37
BZD[f] users, n (%)	15 (55.6)	10 (37.0)	0.43 (0.21 - 0.91)	0.03	21 (32.8)	20 (31.3)	0.89 (0.47 - 1.67)	0.71	0.15
Opioid[g] users, n (%)	11 (40.7)	7 (26.0)	0.49 (0.21 - 1.11)	0.09	22 (34.4)	20 (31.3)	0.86 (0.57 - 1.30)	0.47	0.23
PPI (ATC A02BC) user, n (%)	13 (48.2)	13 (48.2)	1.00 (0.62 - 1.61)	1.00	30 (46.9)	33 (51.6)	1.23 (0.91-1.66)	0.18	0.47
Drug-drug interactions (DDI)									
Clinically significant DDI (class D) (Böttiger et al. 2009), n (%)	2 (7.4)	2 (7.4)	1.00 (0.21 - 4.67)	1.00	1 (1.6)	0 (0.0)	NA	0.32[h]	NA

SD = standard deviation, OR = Odds ratio, CI = Confidence interval, CNS = central nervous system, BZD = benzodiazepine, PPI = proton-pump inhibitor, NA = not available

[a] **Harmful medications** Included **1) Beers Criteria medications [23]**, **2)** [b] **psychotropic medications [52]** (Included [f]*BZDs and related drugs*: ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71; *Antidepressants*: ATC codes N06A, N06CA; [e]*Antipsychotics*: ATC codes N05A, N06CA01); **3)** [c] **Anticholinergic** medications [52]: ATC codes: N04A, N05AA01, N05AA02, N05AB01, N05AB02, N05AB03, N05AB04, N05AC01, N05AC02, N05AF01, N05AF03, N05AF05, N05BB01, N06AA04, N06AA06, N06AA09, N06AA12, N02AG, A03AA, A03AB, A03AX03, A03B, A03CA, A03CB31, A03DA, A03FA01, A04AD01, A04AD12, C01BA01, C01BA03, C01BA51, C01BA71, R03BB, M03B, G04BD, S01FA, R01BA01, R01BA51, R06AB01, R06AE03, R06AE53). If the medication appeared in two or more criteria, they were considered only once.
[d] **CNS medications**: [g]Opioids (ATC codes N01AH, N02A, N02BE51, R05DA, R05FA), [c]anticholinergics [52]; antiepileptics (ATC N03A); [f]BZDs and related drugs (ATC codes N05BA, N05CD, N03AE01, N05CF, A03CA, C01DA70, M05AA51, N06CA01, N02BA71); Antidepressants (ATC codes N06A, N06CA); [e]Antipsychotics (ATC codes N05A, N06CA01).
[h]McNemar test due to zero frequencies. [i]Adjusted for functional ability Rava, CNS medications, GDS-15, MNA

6 DISCUSSION

6.1 IDENTIFYING HIGH RISK MEDICATIONS CAUSING POTENTIAL DRUG-DRUG INTERACTIONS IN OUTPATIENTS: A PRESCRIPTION DATABASE STUDY (STUDY I)

The major implication of this study was to demonstrate that community pharmacists can remarkably influence safe use of medicines in outpatient care by identifying and managing clinically significant DDIs in collaboration with local physicians. There were more than 31,000 potential DDIs in a sample that comprised about 10% of all prescriptions dispensed to outpatients in Finland in one month. Extrapolating the number of clinically significant DDIs in our sample (n=21,538) to all prescriptions dispensed in Finland during that time period indicates that a remarkable number of outpatients were exposed to medications that may have serious clinical consequences. This is an important demonstration that pharmacists can be are a great asset in protecting patients from harm and could be more actively involved in patient care. Pharmaceutical expertise should be more effectively used to manage DDIs and to prevent them, e.g., by finding safer alternatives for drugs that can cause severe interactions. According to the findings of this study, risk for severe DDIs could be substantially decreased simply by focusing on the use of some high risk medications, such as NSAIDs, warfarin, methotrexate, potassium and spironolactone in outpatient care.

According to this study, 10.8% of all prescriptions dispensed during the study period included a potential DDI. Alerts for clinically significant DDIs were found in 7.0% (class C) and 0.5% (class D) of all dispensed prescriptions. This is congruent with previous Nordic studies, which used the same interaction classification (FASS) (Merlo et al. 2001; Heikkilä et al. 2006). In a more recent Swedish study describing the impact of the SFINX database on incidence of potentially serious DDIs in primary care, class D interactions were only found in 0.18–0.22% of prescriptions (Andersson et al. 2013). This may indicate that the use of DDI screening tools has decreased the rate of DDIs. However, changes in the DDI databases are another major explanation for the differences in the DDI rates between the studies. The current SFINX database is more specific than the previously used FASS database (Böttiger et al. 2009). Furthermore, the current SFINX database is structured according to individual substance names, not according to therapeutic groups or ATC codes, which were partially used in the FASS database (Böttiger et al. 2009).

In this study class D interactions occurred most commonly between methotrexate and NSAIDs (36.3% of all class D interaction alerts) and between warfarin and NSAIDs (26.7%). Other common interactions involved fluoroquinolone antibiotics and cations (e.g., iron, calcium) (6.0%), and DDIs

between potassium sparing diuretics and potassium supplements (4.4%). These findings are quite similar to the findings of the previous studies using the same interaction database (Merlo et al. 2001; Heikkilä et al. 2006).

The significance of methotrexate-NSAID interaction is, however, controversial. According to the FASS database, the combination may cause reduction in elimination of methotrexate (FASS 2003). The current Micromedex database still categorizes methotrexate-NSAID interaction as "major" (Micromedex 2015). Many studies have, however, shown that the use of NSAIDs does not have an effect on the kinetics of methotrexate or significantly increase the toxicity in the cure of rheumatoid arthritis (Colebatch et al. 2011). The risk of toxicity is greater in patients receiving high-dose methotrexate for neoplastic disease than in patients receiving low-dose methotrexate. Patients with impaired renal function also appear to be at greater risk (Iqbal et al. 1998). The current Inxbase (previous name SFINX) database categorizes methotrexate-NSAID interaction as class A (no clinical relevance) with enteral methotrexate and class B (clinical outcome of the interaction is uncertain and/or may vary) with parenteral methotrexate. Regarding low-dose methotrexate–NSAID interaction, which represented all the cases in the present study, the current database classifies the interaction in class A (no clinical relevance). Thus, methotrexate-NSAID interaction alerts belong to the limitations of this study.

Warfarin-NSAID interactions have high potential to cause harm to patients (Shorr et al. 1993; Hauta-Aho et al. 2009). Ibuprofen, ketoprofen and acetylsalicylic acid are available in Finland without a prescription. Thus, interactions with warfarin are an underestimate of the actual risk for warfarin-NSAID interactions because OTC-NSAIDs were not identified by the database.

Potassium-potassium sparing diuretic interactions may cause hyperkalemia and arrhythmia, but clinical guidelines, e.g., in the SPCs (Summary of Product Characteristics) of various potassium and spironolactone preparations, recommend monitoring these patients for their potassium values if these drugs are used concurrently.

The most common drug combination in class C interaction alerts was antihypertensive drugs and NSAID (35.3% of class C interactions). Both drugs were among the most commonly used medicines in Finland at the time of the study, which may explain the high interaction rate (Finnish Statistics on Medicines 2004). Regular use of NSAIDs during antihypertensive treatment has shown to raise blood pressure and reduce the effectiveness of many antihypertensives and to increase the risk of myocardial infarction, as well as cause or worsen the symptoms of heart failure (Bleumink et al. 2003; Bavry et al. 2011; Fournier et al. 2014).

This study was conducted using data collected in 2004. A follow-up study using the same method would be useful to show the current DDI prevalence in outpatient care. As our systematic review indicated (see Chapter 2.5.3), internationally, there are not many publications with extensive data, describing the prevalence of DDIs in outpatients. Currently, DDI screening

systems are widely used in Finnish community pharmacies, and DDIs are screened as a part of routine dispensing process (AATE 2017, Kallio et al. unpublished). DDI screening tools are also widely available for physicians, providing support with prescribing. This could be expected to have reduced the prevalence of DDIs. However, community pharmacists have reported need for training, particularly with interpretation and managing of clinical significance of DDIs (Kallio et al., unpublished). Enhanced collaboration and better defined roles and responsibilities of physicians and pharmacists in management of severe DDIs are areas needing action.

6.2 COORDINATING RESOURCES FOR PROSPECTIVE MEDICATION RISK MANAGEMENT OF OLDER HOME CARE CLIENTS IN PRIMARY CARE: PROCEDURE DEVELOPMENT (STUDY II)

This study produced a 5-stage medication management procedure suitable for screening medications of a high number of home care clients and identifying clients with potentially clinically significant DRPs. The model coordinates existing resources with prospective medication risk assessment, an also provides tools to solve identified DRPs. Nurses and PNs' roles in conducting DRP risk assessments, medication reconciliation, and clinical tests during their usual home visits was clarified and reinforced. They also had a key role in implementing and following up medication changes.

Triage meetings was a new and feasible strategy for allocating medication reviews according to clinical needs, while using a minimum of physicians' time. The coordinating pharmacist prepared triage meetings by summarizing each client's DRP risk information from different sources and making preliminary proposals for required actions for physician's consideration. Community pharmacists' contributions changed and became more clinical in the model. They conducted medication reviews and worked closer than before with nurses, PNs and physicians. In future, the coordinating role could be delegated to community pharmacists.

The CoMM model contains an adequate follow-up stage to confirm that the agreed medication changes will actually be implemented and the client's health status monitored. This stage is often missing, though it is crucial for obtaining any benefits from DRP risk assessments and medication reviews (Kiiski et al. 2016).

The model focuses on clinically significant DRPs which may occur due to patient-related factors (e.g., age-related physiological changes, co-morbidities, poor adherence), pharmacological effects of the medications (particularly adverse drug reactions, and high-risk medications) or the medication process of the client (e.g., poor medication management, infrequent follow-ups, various health care providers) (Dimitrow et al. 2014). These are the aspects that PNs were trained to observe during home visits by using the DRP-RAT tool as a guide when communicating with their client or the proxy. Home visits were primarily conducted by clients' own PNs, who knew them. A clinically trained pharmacist conducted home visits only in cases in which risk assessment conducted by a PN indicated serious DRPs requiring more comprehensive investigation. These cases were a minority in our data.

The CoMM development process revealed educational needs both in geriatric pharmacotherapy and for understanding system-based medication risk management. These needs were identified in all participating health care professionals, including physicians and community pharmacists. This kind of model development processes should include interprofessional training that

supports competence and practice development (Holmström et al. 2015a). In our process, home care nursing staff and physicians had training for identifying clinically significant DRPs by using DRP-RAT and deprescribing (Dimitrow et al. 2014, Dimitrow 2016, Page et al. 2016). Community pharmacists were identified requiring training for conducting DRP risk assessments and assuming more responsibility of the triage stage in the future. The coordinating pharmacist was a valuable resource in identifying educational needs and educating staff. Practical nurses were identified to carry a remarkable role in the medication use process of home care clients. In line with findings from a recent national study, home care practical nurses need additional training in pharmacotherapy to meet the requirements of their current work duties in geriatric care (Mononen et al. 2020).

Our experience is that health care teams in home care benefit from having a coordinating pharmacist with qualifications in CMRs, geriatric pharmacotherapy and system-based medication risk management. Our study revealed that organizations and health care units involved in home care clients' medication therapy are working independently in silos, where no specific individual takes holistic responsibility for medications. The same has been found by the Finnish Medicines Agency's program to improve interprofessional collaboration in medicines optimization for older adults (Kallio et al. 2016; Kumpusalo-Vauhkonen et al. 2016). The coordinating pharmacist was needed to facilitate construction of new processes and introduce new tools and approaches in medication management. She scheduled the progression of risk management stages (see Figure 12 and 13) and regularly highlighted the primary goal of the project to those involved: the purpose being to find a feasible way in which to manage and prevent clinically significant DRPs of the home care clients – not to conduct scientific research.

Practitioners involved were not used to working in such close collaboration, which was crucial for the model. Scarce availability of physicians' resources and partly reluctant attitudes towards the new collaborative way of working complicated the arrangement of case-conferences of MRs and CMRs.

System-based risk management perspectives, using Reason's Swiss Cheese Model (Reason 2000) and Hepler and Strand's model (1990) in order to identify and prevent DRPs, were useful in guiding model development and constructing a shared understanding of medication safety and prospective medication risk management. This study indicated that practitioners in Finnish health care are not well acquainted with systems thinking and this requires reinforcement in the future. The same challenge was identified in the WHO report dealing with contributing factors to medication errors in primary care (WHO 2016g).

The strength of using an action research method (Lewin 1946) in model development lies in its ability to consider practical challenges and produce solutions, considering existing resources. The method contributed to the step by step construction of the CoMM model and description of the responsibilities of each professional involved in the model, which is missing in

many other studies (Kiiski et al. 2016). Transferring the model to other home care localities is possible. It will require long-term effort from a qualified coordinator, committed personnel, and managers to reach the mature stage of the collaboration that is necessary for sustainable changes in working patterns. This study used action research method to develop the care coordination model (intervention) and published the development process (Study II), which is a strength of this study.

6.3 IMPACT OF ENHANCED COORDINATION OF CARE ON OUTCOMES OF PROSPECTIVE MEDICATION RISK MANAGEMENT OF OLDER HOME CARE CLIENTS: A RANDOMIZED CONTROLLED TRIAL (STUDY III)

The core of the intervention in this study consisted of triage meetings which proved to be a feasible method for customizing comprehensiveness of collaborative medication reviews (CMRs) for older home care clients according to their clinical needs while minimizing the use of physician's time. Of the older home care clients, 45.5% had no need for more comprehensive medication reviews. Thus, the triage enabled focusing on clients with clinically significant DRPs instead of comprehensively reviewing medications of all clients, as has been the case in many previous studies (Kallio et al. 2018).

The intervention did not show an impact on the use of PIMs between the original intervention group and the control group in the intention to treat analysis, though the per protocol analysis indicated a tendency for effectiveness, particularly in optimizing CNS medication (especially in BZD) use during a 12-month follow-up. As the original IG included many home care clients whose medication changes were not actually implemented as proposed (50% of the intervention group participants), the intervention was incomplete for them. Thus, per protocol analysis is a better predictor of the effectiveness of the coordinated home care model than a comparison between the original intervention group and the control group.

Our baseline findings demonstrate a high prevalence of PIM use. Particularly, the prevalence of potentially inappropriate psychotropic medication use was high (58.1%, n=75) in the entire study population (IG and CG, n=129) included in the intention to treat analysis. Most common was BZD use (41.1%) and antidepressant use (36.4%). National register-based data shows that long-term use of BZDs is the major PIM-related concern in Finland, particularly the use of temazepam (Leikola et al. 2011). A more recent study indicates a declining trend in the long-term BZD use over the last few years (2006–2014), while the long-term BZD use among older adults has remained constant, and at a higher level compared to other populations (Kurko et al. 2018). The decline has not been uniform between the substances: the long- term use of clonazepam and zolpidem has even increased (Kurko et al. 2018). These findings indicate an urgent need for effective deprescribing interventions that should be actively promoted so as to make them part of the routine clinical practice. There are recent promising results of successfully reducing long-term BZD use in older adults through community-based interventions in primary care (Puustinen et al. 2014; Puustinen et al. 2018).

Inappropriate use of antipsychotics (APs) is another major concern in geriatric pharmacotherapy, which can also be seen in our data (baseline users: 15.5%, n=20). APs are usually prescribed for behavioral and psychological symptoms of dementia though the use may even continue for years without

proper follow-ups (Jalava et al. 2018). International criteria, e.g., Beers Criteria, have updated their recommendations on the use of APs in recent years: use should be avoided unless nonpharmacological options have failed or are not possible and the individual is threatening substantial harm to self or others (AGS 2015, AGS 2019). However, Finnish guidelines are not as strict concerning AP use in older adults as the most recent international guidelines (Fimea 2019, Meds75+). This may partly explain their wide use among older outpatients and inpatients in Finland (Jalava et al. 2018). It would be important to reconsider our domestic guidelines and care practices to meet current international standards of AP use.

Another contributing factor to excessive use of antipsychotics in older adults is culture of care (Nurminen et al. 2009; Sawan et al. 2018). Our experience in Lohja Home Care was that some of the physicians and nurses were reluctant to actually stop the AP treatment even though the potential need for deprescribing was agreed on in the triage meeting. As previous studies have shown, this may be due to concerns regarding stopping medications started and prescribed by other physicians, limited knowledge of how to stop APs and concerns regarding a relapse of behavioral disorders (Reeve et al. 2016; Bjerre et al. 2018; Sawan et al. 2018). Further research is needed to better understand these systems-based factors influencing AP use which can lead to unnecessary and harmful long-term medications.

Implementation of the intervention

We experienced challenges in implementing the new procedure. This was also seen in the analysis of the effectiveness of the intervention. Physicians' limited resources, partly reluctant attitudes, and weak engagement to the new, more collaborative medication management practice were evaluated as the main contributing factors for the intervention not being fully implemented. Some physicians were reluctant and did not approve of and implement any of the recommended clinically significant medication changes. Thus, these factors affecting medicines optimization require further investigation.

This trial represents the real world and includes features of pragmatic trials, which frequently include complex interventions, involving the skills and experience of various health care providers to deliver the intervention (Ford & Norrie 2016). Our experience is that implementation of this kind of new coordinated procedure requires long-term and goal-oriented commitment of all healthcare providers involved, in order to break organizational barriers and change working behaviors and patterns. Educational needs in both geriatric pharmacotherapy and understanding system-based medication risk management were identified in all participating health care providers, including PNs, nurses, physicians and community pharmacists. The most striking competence gap observed relates to deprescribing. Thus, a better deprescribing protocol needs to be used in future studies.

6.4 RELIABILITY AND VALIDITY OF THE RESEARCH METHODS (I-III)

Study I

This study has some advantages compared to previous DDI incidence studies (see Table 10). The study sample was quite large and covered all age groups of Finnish medicine users in outpatient care from different parts of the country (11 locations across the country). Some of the previous studies gathered their data from only two or three cities (Heikkilä et al. 2006; Chatsisvili et al. 2010) or from one province of the country (Astrand et al. 2007; Lopez-Picazo et al. 2010). Furthermore, some studies had remarkably smaller sample sizes compared to this study (Heikkilä et al. 2006).

Although the data were collected quite a long time ago, the study is still relevant. According to the systematic literature review that we recently conducted on DDI incidence studies in outpatients, few studies have focused on community pharmacy settings (Table 11). Publishing the results of this study will facilitate comparisons with more recent data to indicate whether any improvements have taken place in safety of medication use in outpatients in terms of clinically significant DDIs.

This study focused solely on DDIs and the service development regarding the DDI-surveillance system available 16 years ago. With current databases and surveillance systems it is possible to also identify other risks, such as drug-disease, drug-food or drug-herbal product interactions. If these other potential risks were to be screened in the community pharmacy, the same kind of collaborative service model needs to be developed with the local health care providers as developed for DDIs in this study. Aspects that need to be agreed upon include: how to coordinate utilization of the surveillance system; in which cases pharmacists can manage DDIs and when they should contact the prescribers and how the potential risks should be communicated with the patients.

As the surveillance system did not take into consideration the timing of dispensing of the drugs, it is not known whether the interacting drugs were used concurrently, which is a prerequisite for an actual interaction to occur. Therefore, this study may overestimate the number of actual DDIs occurring. In 50.0% of all interactions in this study, both drugs were dispensed between April and July. In such cases at least, drugs for long-term therapies were most likely still in use. Even though the interacting drugs may have been used concurrently, it is not known whether they resulted in any harm to the exposed patients. Some studies conducted in hospitals have estimated that 10–50% of potential DDIs are clinically significant on patients (Wiltink 1998). A Finnish study on DDIs between warfarin and cisapride revealed that over 70% of theoretical interactions caused some clinical changes or harm to patients (Laine et al. 2000).

The data contained only the total number of dispensed prescriptions, not for any individual drugs. Thus, it was not possible to ascertain the ratio of observed interactions for a drug and its total dispensing rate.

The data was also incomplete because it did not include drugs sold over the counter (OTC). There are many OTC drugs with a potential to interact with prescribed medicines. These include ibuprofen, ketoprofen and acetylsalicylic acid (NSAIDs). According to a Finnish study, 4% of OTC drug users had taken a drug combination with a potential for a clinically significant drug interaction (Sihvo et al. 2000). These potential interactions between OTC drugs and prescribed medicines are missing from this study. In addition to previous limitations, interactions were only screened between drugs dispensed from the University Pharmacy outlets. It is known that consumers use different pharmacies, thus interactions between drugs dispensed from pharmacies other than the University Pharmacy outlets were undetected in this study.

Study II

System-based risk management approaches using Reason's Swiss Cheese Model (Reason 2000) and Hepler and Strand's model (Hepler and Strand 1990) to identify and prevent DRPs, were useful in guiding model development and constructing a shared understanding of medication safety and prospective medication risk management. Our study indicated that practitioners in Finnish health care are not well acquainted with systems thinking, a fact which need to be addressed in the future.

The strength of using an action research method (Lewin 1946, Meyer 2000) in model development lies in its ability to consider practical challenges and produce solutions, taking existing resources into consideration. The method contributed to the step by step construction of the CoMM model and description of the responsibilities of each professional involved in the model, which is missing from many other studies (Kiiski et al. 2016).

Study III

Strengths and limitations of the methods

This study produced an RCT with a combination of outcome measures to assess general health status and functional ability of older adults, and also targeted to symptoms suggestive of adverse effects of medications.

Our study design and randomization strategy worked well. At baseline, the characteristics of the participants in the IG and the CG were similar, despite functional ability (Rava) and use of antiepileptics, which were adjusted in the ITT-analyses. We used cluster randomization to avoid contamination related to home care nurses and PNs. Contamination related to community pharmacists and physicians was not considered, since these professionals did not have regular encounters with the home care clients. Clustering by service area was not accounted for in the data analysis.

We selected outcome measures and follow-up periods which have been proven appropriate in previous studies (Kiiski et al. 2016; Huiskes et al. 2017; Kallio et al. 2018). A 12-month follow up period has shown to be long enough to implement medication changes, demonstrate potential changes in study participants' health outcomes and sustainability of changes made in their medications (Kiiski et al. 2016). Selected measures were congruent with recent studies proposing core outcome measures for trials aiming to improve appropriate medication use in older adults (Beuscart et al. 2018; Rankin et al. 2018a). Our goal in future research is to investigate whether there is an association between the intermediate measures used in this study (medication risks) and improved health/function/cognition outcomes.

A limitation of this study is the relatively small sample size, which may have affected the weak effectiveness of the intervention. Half of the eligible residents did not provide written consent to participate. High workload of the recruiting nursing staff, as well as frail and multi-morbid home care clients were evaluated as main contributing factors. The high attrition rate during the first study year, due to old age and multiple morbidities of the participants also contributed to the small sample size. In future studies with multi-morbid and frail older adults, these methodological issues crucially influencing the power of the study needs to be better considered. The same has been observed in other studies with multi-morbid older adults (Juola et al. 2015).

We included in the analysis only participants with baseline and 12-month follow-up data available (Dumville et al. 2006). Poor implementation of recommended medication changes was the rationale for conducting per protocol analyses, including only participants with at least one clinically significant medication change actually implemented. As we were able to show a tendency for effectiveness in the per protocol analysis, it would be important to repeat the intervention with larger study populations to confirm the findings.

This demonstration study was carried out by including only one community pharmacy operating in Lohja in the intervention. This strategy was chosen to keep the study design simple, as adding more community pharmacies to the study would have increased risk of bias. It would be important to repeat the intervention in the home care of other municipalities and involve other community pharmacies in future research.

6.5 PRACTICAL IMPLICATIONS

Study I was undertaken to support implementation of the first online DDI surveillance system in Finnish community pharmacies. The study is a demonstration of how community pharmacies can use information provided by their surveillance system for risk-management research purposes and their own service development. This study described the new service model developed by a national community pharmacy operating in 17 locations (in 2004) across Finland, in co-operation with local physicians. The service development was initiated by identifying the most common and clinically significant DDIs and their prevalence rate. This evidence laid the foundation for establishing in-house guidelines for managing DDIs within the University Pharmacy.

The same kind of strategy as applied in this study to integrate community pharmacists' contribution to DDI management could be used for implementing other patient-care-oriented services. Such services could relate to implementation of other screening tools for medication risk loads, extended to cover, e.g., anticholinergic and serotonergic loads, and PIM use in older adults. Community pharmacies have advanced tools and willingness to participate more systematically in medication risk management (Jokinen et al. 2019). The remaining challenge is how their contributions can be increased and integrated into the collaborative medication use process (Kallio et al. 2018). Their contributions could add to scarce resources available in primary care to manage medications of a growing number of older people.

Studies II–III

The developed CoMM procedure is feasible for screening and reviewing medications of a high number of older home care clients to identify clients with severe DRPs and provide interventions to solve them utilizing existing primary care resources. The coordinating pharmacist was required to facilitate the construction of new processes and introduce new tools and approaches in medication management, while other health care practitioners worked as a part of their normal clinical work.

Our experience was that health care teams benefit from having a coordinating pharmacist with qualifications in CMRs, geriatric pharmacotherapy and system-based medication risk management. Our study revealed that each organization and health care unit involved in home care clients' medication therapy is still today working independently in silos, where no individual assumes holistic responsibility for medications.

The CoMM study was a demonstration study showing preliminary and promising positive results. The procedure can be transferred to other home care units and adopted to their local circumstances. The procedure could be particularly designed to reduce CNS use in older adults, as it is among the major problems in geriatric pharmacotherapy in Finland (Leikola et al. 2011,

Juola et al. 2015; Pitkälä et al. 2015; Hyttinen 2018; Jalava et al. 2018; Kurko et al. 2018; Vartiainen et al. 2018).

The triage method used in the CoMM proved to be a feasible method for customizing comprehensiveness of collaborative medication reviews for older home care clients according to their clinical needs, while minimizing the use of physicians' time. Physicians' resources were only needed for identified clinically significant DRPs requiring intervening action, while in nearly 50% of the cases physician resource was not needed. The triage method should be more widely used to identify and solve drug-related problems in older home care clients. The utilization of artificial intelligence in the screening stage in future is under way.

During this study, much was learned about conducting an implementation and intervention study. Few studies of this kind have been carried out in Finland. However, implementation and intervention studies are important for learning from the organization of Finnish health and social care, particularly how primary care works and what the development needs there are. This study has produced remarkable information and evidence on Finnish health care, particularly home care, and contributed many new research projects. Results have had many practical implications, e.g., in developing the Rational Pharmacotherapy Action Plan 2018–2022 established in 2018 (Ministry of Social Affairs and Health 2018). Furthermore, the experience of this study is used in developing professional services for pharmacies, and developing undergraduate, specialization, accreditation and other continuing education (including the development of medication review practices and the criteria for competencies they require) (AATE 2017). Data from the study have also been utilized in other studies, such as the use of QT-prolonging drugs (Skullbacka 2019), deprescribing (Nurminen 2019), systemic factors contributing excessive polypharmacy and prescribing cascade (Luoma 2018).

6.6 FUTURE RESEARCH

Related to managing DDI risks, future research is needed to assess whether any changes have occurred in the incidence and type of clinically significant DDIs in primary care patients during the past 16 years. Our updated systematic review on DDI studies evidenced that there is still not much research on DDIs in outpatients in primary care. Furthermore, it would be interesting to study how this service model to collaboratively manage DDIs has changed community pharmacists' practice and their cooperation with physicians. It may also have a spillover effect on physicians' prescribing.

With the CoMM procedure, we were able to show a tendency for effectiveness in the per protocol analysis, and it would thus be important to repeat the intervention with larger study populations in order to confirm the findings. It would also be important to repeat the intervention in the home care of other municipalities.

In future, utilization of artificial intelligence in the screening of medication risks is a potential and useful area of research.

Further studies are needed on care culture and other contributing factors to high prevalence of PIM use and other risks for clinically significant DRPs identified in this study. Particularly, physicians' reluctance to implement recommended medication changes in cases of inappropriate polypharmacy, and relationships between inappropriate medication use and medication errors require further investigation. Particularly, further investigation on system-based factors contributing to situations where identified preventable clinically significant medication risks are left unsolved is required.

7 CONCLUSIONS

- Study I demonstrated that community pharmacies can actively contribute to DDI risk management and systematically use their surveillance systems for identifying patients having clinically significant DDIs. The findings also indicated that the majority of potentially serious (class D) interactions in outpatients involved a limited number of drugs, particularly NSAIDs, warfarin and methotrexate.

- In Study II, the developed care coordination intervention (CoMM) was feasible for screening and reviewing medications of a high number of older home care clients to identify clients with severe DRPs and provide interventions to solve them utilizing existing primary care resources.

- Triage meetings proved to be a feasible method for customizing collaborative medication reviews according to home care clients' clinical needs, while minimizing physician's time demands. Of the clients, 45.5% had no need for more comprehensive medication reviews. Thus, the triage enabled focusing on clients with clinically significant DRPs instead of comprehensively reviewing medications of all clients, as has been the case in many previous studies.

- In Study III, the intervention (CoMM) indicated a tendency for effectiveness when implemented as planned, particularly in optimizing CNS medication use during a 12-month follow-up.

- This study demonstrates the challenges that have to be overcome when trying to change clinical practice and improve coordination between units involved in medication management of home care clients. Even though the outcomes of the intervention were not optimal, the value of the study is in discussing the real world experiences and challenges of implementing new practices in home care. Our study indicated that practitioners in Finnish health care are not well acquainted with systems thinking and this needs reinforcement in the future.

- Community pharmacists' contribution to medication safety, particularly in older adults, should be better utilized in the future, as this thesis shows promising demonstrations. Health care teams in home care could benefit from having a coordinating pharmacist with qualifications in CMRs, geriatric pharmacotherapy and system-based medication risk management, to facilitate construction of new processes.

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