Clinical Pharmacy Group
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DEVELOPING SAFE MEDICATION PRACTICES WITHIN A REGIONAL HEALTH CARE DISTRICT IN FINLAND

Ercan Çelikkayalar

ACADEMIC DISSERTATION

Doctoral thesis, to be presented for public examination with the permission of the Faculty of Pharmacy of the University of Helsinki, in Auditorium, Satasairaala Central Hospital, Pori on the 3rd of June, 2022 at 12 o'clock

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ABSTRACT

Medication safety has become one of the most highlighted areas of patient safety since medication errors (MEs) are common in all care settings (WHO 2017; FIP 2020). MEs may lead to severe adverse drug events (ADEs), including adverse drug reactions (ADRs). Based on a growing body of research evidence, policy recommendations during the last decades have raised awareness about the occurrence and consequences of MEs within health care systems. In these recommendations, health care organizations have been called for action to build up safe medication practices at national, regional, organizational, and patient care levels.

This doctoral thesis aims to build up safe medication practices within a regional health care district in Finland. The practices included in this thesis were selected from three different operational levels of the system: 1) organizational level; 2) health care unit and clinical practice level; 3) patient care and medication use level. The thesis had the following three objectives: I. To develop and validate a medication safety self-assessment tool (MSSA) in secondary care hospital wards *(Study I: organizational level);* II. To use clinical pharmacist-conducted collaborative medication reviews (CMRs) in an emergency department (ED) short-term ward to identify inappropriate prescribing (IP) in pre-admission medications; *(Study II: health care unit and clinical practice level);* III. To investigate how well older people are aware of the major potential risks of benzodiazepines and related drugs (BZD) they are taking and whether the risk awareness changed between 2004 and 2015 *(Study III: patient care and medication use level).* This doctoral thesis applied a systems approach to medication risk management based on the Theory of Human Error as a theoretical framework (Reason 2000).

This doctoral thesis consists of a literature review and three empirical studies (Studies I-III). The literature review focused on identifying and describing algorithms used to assess the causality and preventability of adverse drug reactions/ adverse drug events (ADRs/ADEs) in hospital settings. The first part of the literature review systematically summarized studies using standardized algorithms to measure the causality and preventability of ADRs/ADEs (covered publications from 1990-2010). The second part of the literature review covered more recent studies from the years 2011-2020 that focused on the two most commonly used algorithms for assessing causality and preventability of ADRs/ADEs.

In **Study I** *(organizational level)*, the Medication Safety Assessment Tool for Hospitals (MSSA) by the Institute for Safe Medication Practices (ISMP) was adopted and remodeled for Finnish hospital settings by the Delphi consensus method. The original MSSA tool (231 items under ten components) was first modified preliminarily and then by the Delphi expert panel (14 panelists) with four rounds. A total of 114 items (91 original items + 23 new items) were accepted and remodeled

by organizing the items into a new order (under six new components), which is consistent with the ward-based pharmacotherapy plan recommended by the Finnish Ministry of Social Affairs and Health (MSAH) (MSAH 2006). The modified MSSA tool was then pilot tested on 8 hospital wards of various specialties in a regional secondary care hospital. Several safety recommendations were documented, including the development of clinical pharmacy services.

In **Study II** (*health care unit and clinical practice level*), pre-admission medications of all adult patients admitted to the emergency department's (ED) short-term ward during the five-month study period were reviewed by the pharmacist in collaborative medication reviews (CMRs). The study was conducted in the same regional secondary care hospital as Study I. Types of inappropriate prescribing (IP) were analyzed, and 113 IP events were identified in 83 (9.7%) of the patients (n=855). As the majority (81%, n=67) of these patients were older adults (≥65 years), the further descriptive analysis of IP events was targeted to this age segment. The three main types of IP events were misprescribing (79% of the identified and 72% of the confirmed IP events), over-prescribing (15% vs. 21%), and underprescribing (6% vs. 7%). Benzodiazepines and related drugs (BZD) (29%) and antidepressants (28%) were involved in 33 out of 58 (57%) confirmed IP events. Medications with strong anticholinergic effects were involved in 19% of the confirmed IP events.

In **Study III** (*patient care and medication use level*), the risk awareness of older BZD users was investigated using two cross-sectional patient data sets collected from a public primary care hospital within the same health care system in one month in 2004 (n=37) and 2015 (n=31). The study patients were personally interviewed to determine how well they were aware of the potential risks of the BZD they were taking and whether the risk awareness had changed in the years between the two study periods. The study found that awareness of dependence (p=0.047), interaction with alcohol (p=0.001), dizziness (p=0.002), and developing tolerance (p=0.002) had improved, while awareness of the other potential risks remained unchanged.

This thesis found that the modified and validated MSSA tool can be used to support building up safe medication practices in health care organizations, particularly establishing ward-based pharmacotherapy plans as guided by the MSAH (Study I). The pharmacist-led CMR practice was found helpful in ED admissions for older residents (>65 years) using BZD and drugs with strong anticholinergic effects: they should be paid special attention in ED admissions (Study II). Older BZD users' awareness of potential risks related to BZD use was improved between 2004 and 2015. Despite improved patient awareness, no significant change was found in their willingness to discontinue BZD therapy (Study III). National-level coordination is needed to integrate the modified MSSA tool for hospitals as a part of national patient safety policies in Finland (Study I). More research is required to assess whether CMR practice in the ED could impact preventable ED re-admissions (Study II). Future research should also investigate patients' risk awareness of different high-risk medications, especially in older users (Study III).

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Hämeenlinna, May 2022

Ercan Çelikkayalar

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This doctoral thesis is based on the following peer-reviewed publications:

I. **Celikkayalar E**, Myllyntausta M, Grissinger M, Airaksinen M. Adapting and remodeling the US Institute for Safe Medication Practices' Medication Safety Self-Assessment tool for hospitals to be used to support national medication safety initiatives in Finland. Int J Pharm Pract. 2016;24(4):262-70. doi: 10.1111/ijpp.12238.

II. **Celikkayalar E**, Puustinen J, Palmgren J, Airaksinen M. Collaborative medication reviews to identify inappropriate prescribing in pre-admission medications at emergency department short-term ward. Integr Pharm Res Pract. 2021;10:23-32. doi: 10.2147/IPRP.S280523.

III. **Celikkayalar E**, Airaksinen M, Kivelä SL, Nieminen J, Kleme J, Puustinen J. Are older people aware of potential risks related to benzodiazepines they are taking and has anything changed in risk awareness over ten years? Patient Prefer Adherence. 2021;15:141-147. doi: 10.2147/PPA.S280503.

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 2006). The definition includes adverse drug reactions (ADRs) and medication errors (MEs).

Adverse drug reaction (ADR)
Any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy (WHO 1969, Council of Europe 2006).

Collaborative medication review (CMR)
Medication review practices involving pharmacists as reviewers of the medication in close collaboration with other health care professionals (Ministry of Social Affairs and Health (MSAH 2011).

Drug-drug interaction (DDI)
The ability of one drug to enhance, diminish and/or modify the action or effects of another drug when administered successively or simultaneously (Askari et al. 2013).

Health care district (in Finland)
Finland is divided into 21 hospital districts. Each district is responsible for the provision of municipal secondary care services. Each municipality must be a member of one hospital district. Hospital districts are financed and managed by the member municipalities. Each municipality also is responsible for providing primary health services for its residents. In this study, we used the term Health care district that includes both primary and secondary care services within the hospital district (Ministry of Social Affairs and Health of Finland, MSAH 2021a).

High-alert medication (High-risk medication)
Drugs that bear a heightened risk of causing significant patient harm when used in error (for example wrong drug, wrong dose, wrong route). Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients (Institute for Safe Medication Practices ISMP 2010, ISMP 2014).

Inappropriate prescribing (IP)
Prescribing medications that have more potential risk than potential benefit or prescribing that does not agree with accepted medical standards (Hanlon 2001).

Medical error
An adverse event or near miss that is preventable with the current state of medical knowledge (World Health Organization WHO 2009).

Medication error (ME)
Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is controlled by the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use (National Coordinating Council of Medication Errors Reporting, NCC MERP 1998).

Medication review
A structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of drug-related problems, and reducing waste (Clyne et al. 2008).

Medication risk management
A strategy that aims to prevent or decrease risks associated with the use of medicines (Cohen 2007).

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 2005 and 2006, World Health Organization, WHO 2009 and 2017).

Older adults (older persons, elderly)
Most developed countries have accepted the chronological age of 65 years as an age limit of 'elderly' or older persons (United Nations 2019). The thesis applies this definition.

Patient safety
Freedom from accidental injuries during the course of medical care, activities to avoid, prevent, or correct adverse outcomes which may result from the delivery of health care (Kohn et al. 2000, Council of Europe 2005, World Health Organization 2009).

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, excessive polypharmacy ten or more medications (Masnoon et al. 2017; World Health Organization 2019).

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

Prescribing error
A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice (Dean et al. 2000).

ABBREVIATIONS

ADE	Adverse drug event
ADR	Adverse drug reaction
CMR	Collaborative medication review
BZD	Benzodiazepines and related drugs
ED	Emergency Department
DDI	Drug-drug interaction
Fimea	Finnish Medicines Agency
GI	Gastrointestinal
IP	Inappropriate prescribing
ISMP	Institute for Safe Medication Practices (United States)
ME	Medication error
MMSE	Mini-Mental State Examination
MSAH	Ministry of Social Affairs and Health (Finland)
MSSA	Medication Safety Self-Assessment
NSAID	Non-steroidal anti-inflammatory drug
PIM	Potentially inappropriate medicine
PRN	pro re nata (when required)
Turku CRC	Turku Clinical Research Centre
WHO	World Health Organization
WHO-UMC	World Health Organization, The Uppsala Monitoring Centre

1 INTRODUCTION

Medication safety is an essential part of patient safety. Two decades ago, one of the most widely recognized reports on patient safety, To Err is Human by the US Institute of Medicine (2000), explained how medical errors, and medication errors (ME) as part of them, occur and how to prevent them. The report has created awareness and encouraged health care providers, governments, and medical societies globally to develop tools for measuring and improving safety in health care (Kohn et al. 2000). In the report To Err is Human, safety was defined as "freedom from accidental injury and error as a failure of a planned action to be completed as intended or using a wrong plan to achieve a goal." An error may or may not cause an adverse event. Adverse events result from a medical intervention and are responsible for harm to the patient (Kohn et al. 2000).

Medications are the most frequent cause of adverse events, and such injuries are called adverse drug events (ADEs) (Leape et al. 1991, Bates et al. 1995). MEs may lead to ADEs, and ADEs may result in severe injuries, even death. ADEs may be preventable or not preventable. However, ADEs caused by the MEs are always preventable (Kohn et al. 2000, Morimoto et al. 2004). To identify and prevent MEs, it is crucial to state which specific medication practices are responsible for the ADEs in routine practice (Kohn et al. 2000; Council of Europe 2006, WHO 2017).

In 2017, the World Health Organization (WHO) released the third Global Patient Safety Challenge and raised medication safety into focus with the program "Medication without Harm" (WHO 2017). The Program highlighted that unsafe medication practices are a leading cause of preventable harm in health care systems across the world. According to the WHO report, globally, the cost associated with MEs has been estimated at 42 billion USD annually (WHO 2017). The WHO report states that MEs occur when weak medication systems and human factors adversely affect prescribing, transcribing, dispensing, administration, and monitoring practices, resulting in severe harm, disability, and even death (WHO 2017). The program "Medication Without Harm" aimed to reduce the level of severe preventable harm related to medication by 50% over five years globally (during the period 2017-2022). The critical areas of the challenge are high-risk situations, particularly in hospital settings involving the use of complex medications, high-risk patients (especially older adults with high-risk medications), polypharmacy, and transitions of care (WHO 2017).

In Finland, the first national medication safety initiatives to reduce MEs were introduced in 2006 when the Finnish Ministry of Social Affairs and Health (MSAH) developed guidelines for safe medication practices in public and private social and health care units (MSAH 2006), later updated in 2016 and 2021 (MSAH 2021b). The core of the guidelines is to instruct each health care unit to establish its pharmacotherapy plan that serves as a tool for defining and implementing key

medication safety actions appropriate for that particular unit. Among many other recommendations in the guidelines, active participation of pharmacists to improve medication safety was highlighted.

Collaborative medication reviews (CMR) with pharmacist participation have been suggested to improve medication safety by reducing inappropriate prescribing (IP) (Rankin et al. 2018). An earlier systematic review (ten studies) from 2016 showed that CMR may reduce emergency department (ED) contacts (Christensen and Lundh 2016). A randomized study (1467 patients) showed that CMR likely reduces the number of ED visits and hospital readmissions (Ravn-Nielsen et al. 2018). Because ED is the care unit where acutely ill patients are first examined, it is also where drug-induced symptoms and events can be identified. Therefore, CMR in EDs can be a point of care to identify IP in pre-admission medications, mostly taken at home (Dresden et al. 2018). For example, the geriatric ED guideline by The American College of Emergency Physicians suggests that CMRs should be initiated early in the ED (American College of Emergency Physicians 2013). However, only a few recent studies have explored CMRs in the ED units (Hohl et al. 2017, Liu et al. 2019, Schepel et al. 2019, Kitchen et al. 2020). Liu et al. found that significant polypharmacy and use of potentially inappropriate medications (PIM) such as benzodiazepines and related drugs (hereafter collectively BZD) were lower in the post-intervention group with CMR than in the pre-intervention group without CMR (Liu et al. 2019).

BZD are widely used PIMs (American Geriatrics Society 2019). Their use is recommended to be avoided in older adults because of growing evidence on the harmful adverse effects of BZD (The Finnish Medical Society, Duodecim 2015; American Geriatrics Society 2019, Finnish Medicines Agency, Fimea 2021). A few earlier studies have explored the patients' perceptions and experiences of their BZD use (Iliffe et al. 2004, Cook et al. 2007, Sirwardena et al. 2008, Sake et al. 2019). BZD users may usually think that their BZD medication is helpful and effective; however, at the same time, they may underestimate or even may not be aware of the potential risks related to BZD, especially if the use is long-term (Puustinen et al. 2007; Lähteenmäki et al. 2014; Webster et al. 2017; Sake et al. 2019). Age appears to be one of the major contributing factors to risk perception because older people have lower perceptions of risk (Webster et al. 2017). A better understanding of perceived risks about BZD use would help health care professionals to support their patients' safe use of BZD. Although recent studies have investigated the risk perceptions of BZD users (Iliffe et al. 2004, Sirwardena et al. 2008, Sake et al. 2019), risk awareness of BZD users, i.e., what they actually know about the potential risks, is not well understood.

This doctoral thesis includes a literature review that aims to identify studies using standardized algorithms to assess the causality and preventability of adverse drug events (ADEs), including adverse drug reactions (ADRs) as a subset of ADEs. Standardized algorithms are methods, which apply specific questions and resulting scores to determine the likelihood of a cause-effect relationship between the drug and an ADR/ADE (Hutchinson et al. 1983, Agbabiaka et al. 2008). The purpose of

the literature review was to better understand the nature of ADEs as a starting point of the empirical part of the thesis.

The empirical part of the thesis focuses on building up safe medication practices in a regional health care context. It consists of three studies concerning the following practices: a Delphi-consensus study to develop a medication safety self-assessment (MSSA) tool for the hospitals (Study I), a prospective cross-sectional study to identify IP in pre-admission medications at ED by using a CMR practice (Study II), and a descriptive study based on personal patient interviews including two cross-sectional data sets to investigate how well older people are aware of the potential risks related to the BZD they are taking and whether the risk awareness has changed between the years 2004 and 2015 (Study III).

2 REVIEW OF THE LITERATURE: USING PRE-DETERMINED ALGORITHMS TO ASSESS CAUSALITY AND PREVENTABILITY OF ADVERSE DRUG REACTIONS AND ADVERSE DRUG EVENTS

According to the WHO, an adverse drug reaction (ADR) is any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy (WHO 1969, Council of Europe 2007). Thus, the term ADR describes harm caused by a drug's pharmacological properties. The term adverse drug event (ADE) also covers other adverse events that relate to drug use. As defined by the Council of Europe, ADE is any injury occurring during the patient's drug therapy and resulting either from inappropriate care or from unsuitable or suboptimal care. Thus, ADEs include ADRs during normal use of the medicine and any harm secondary to a medication error, both errors of omission or commission (Council of Europe 2007). The Institute of Medicine's definition of an ADE is more direct: an injury resulting from medical intervention related to a drug (Kohn et al. 1999). Therefore, it is essential to understand the terms and the difference between ADRs and ADEs, and their relationship with medication errors (MEs) (Figure 1).

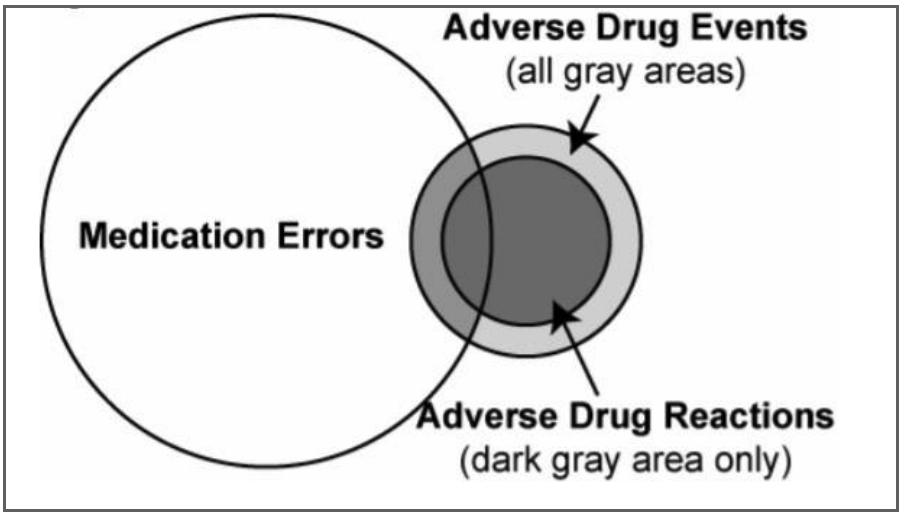


Figure 1. Relationship of MEs, ADEs, and ADRs as presented in 2004 (Nebeker et al. 2004). The grey areas represent injuries caused by drug use (ADEs). The dark grey area represents harm caused by a drug, describing ADRs. The intersection area of the two circles ADEs and MEs, represent preventable harm. The remaining area in the ADE circle represents non-preventable harm, and the remaining area in the ME circle represents no harm.

WHO defines a medical error as an adverse event or near miss that is preventable with the current state of medical knowledge and medication errors are the most common medical errors and can induce adverse events (WHO 2009). A medication error is described as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is controlled by the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems (National Coordinating Council of Medication Errors Reporting, NCC MERP 1998).

A landmark early phase study found that ADEs occurred in approximately 6% of all admitted adult patients and that 28% of these were preventable (Bates et al. 1995). Throughout the years, the estimated frequency of the ADE occurrence remained the same (approximately 5%); and the estimated percentage of the preventable ADEs remained significantly high in both outpatient and inpatient settings (Winterstein et al. 2002, Kanjanarat et al. 2003, Krähenbuhl-Melcher et al. 2007, Thomsen et al. 2007, Bourgeois et al. 2010, Leendertse et al. 2010, Hakkarainen et al. 2012a, Lo Giudice et al. 2019).

As a subset of ADEs, ADRs are also common. According to a 1998 meta-analysis (Lazarou et al. 1998), 6.7% of hospitalized patients had a serious ADR (occurring while in the hospital or causing admission to the hospital) with a case fatality rate of 0.32%. This ADR-related hospitalization rate was higher than the hospitalization rate for pulmonary disease, diabetes, or automobile accidents in the same study. Another meta-analysis in 2002 (Beijer et al. 2002) estimated that 4.9% of hospital admissions were ADR-related, with people over 65 years of age being at the highest risk. Another meta-analysis published in 2012 (Hakkarainen et al. 2012a) found that 2% of adult outpatients hospitalized or accessing emergency care had experienced preventable ADRs. In that meta-analysis, half of the ADRs in outpatients and nearly half of those in inpatients were estimated to have been preventable. A very recent (2021) systematic review and meta-analysis identifying thirty-three studies (with a total study population of 1,568,164 individuals) found the prevalence of ADRs in the primary care setting being 8.3%, and the percentage of preventable ADRs ranging between 12-38% (Insani et al. 2021). Another recent (2020) systematic review and meta-analysis, identifying 27 studies, found an ADR prevalence of 16% in a population of 20,153 hospitalized patients aged ≥65 years (Jennings et al. 2020).

To state whether the ADR/ADE is preventable or not, as a first step, the potential cause-effect relationship between medication and an ADR/ADE must be identified. In some studies, potential ADR/ADE causality was assessed through patient interviews or expert judgments (Miremont et al. 1994, Arimone et al. 2005). However, researchers have questioned the reliability of expert judgments about the suspected causality, noting failed attempts at reproducing the results (Benichou et al. 1993, Arimone et al. 2005). A systematic review in 2008 identified 31 different causality assessment methods and grouped them into three main categories: (i) Expert Judgement/Global Introspection; (ii) Algorithms; and (iii) Probabilistic Methods (including Bayesian Approaches) (Agbabiaka et al. 2008). Algorithms are standardized methods, which apply specific questions and resulting scores to

determine the likelihood of a cause-effect relationship between the drug and an ADR/ADE. Twenty-six of the 31 methods presented in the review were algorithms. Although algorithms lack flexibility, they are considered more reliable than individual expert judgments (Naranjo et al. 1981, Hutchinson et al. 1983, Agbabiaka et al. 2008). Another systematic review (2012) identified 18 instruments organized into four categories for determining the preventability of ADRs: 1) instruments using only a definition of preventability; 2) instruments with both a definition of preventability and an assessment scale for determining preventability; 3) instruments with specific criteria for each preventability category; and 4) instruments with an algorithm for determining preventability (Hakkarainen et al. 2012b).

Reliable methods for assessing both causality and the preventability of ADEs are needed to better understand the nature of ADEs. This literature review aimed to identify studies using standardized algorithms to measure both the causality and preventability of ADEs.

The literature review consisted of two stages. The first stage of the review, which was conducted as a systematic review, identified studies using standardized algorithms to measure both the causality and preventability of ADEs between 1990-2010. The second stage of the review was a literature review of the studies published between 2011-2020, using the most common algorithms: the Naranjo scale (Naranjo et al. 1981) for the causality assessment and Schumock and Thornton criteria (Schumock and Thornton 1992) for the preventability assessment of ADEs. The key objectives of this review were to evaluate the evidence on causality and preventability of ADRs/ADEs.

2.1 Stage I: A systematic review of the studies between 1990-2010 (using various algorithms)

2.1.1 Search strategy and data extraction

An electronic search was performed in MEDLINE, IPA (*International Pharmaceutical Abstracts*), CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), and the COCHRANE databases. Articles were searched from January 1990 to December 2010 using the terms "Adverse drug reaction" or "Adverse drug event" or "Medication error" or "Drug-related problem" in combination with "Preventability" or "Avoidability." MeSH terms were used, where appropriate, in combination with search terms. In addition to search terms ADR and ADE, the additional terms, drug-related problem (DRP), and medication error were also used because MEs or ADEs may lead to DRPs. A drug-related problem (DRP) *is any undesirable event experienced by a patient that involves or is suspected to involve drug therapy, and that interferes with achieving the desired goals of the therapy* (Cipolle et al. 2004).

The electronic search resulted in 241 publications. The search protocol is presented in Figure 2. After duplications were excluded, 168 publications of the 241 remained to be screened (Figure 2).

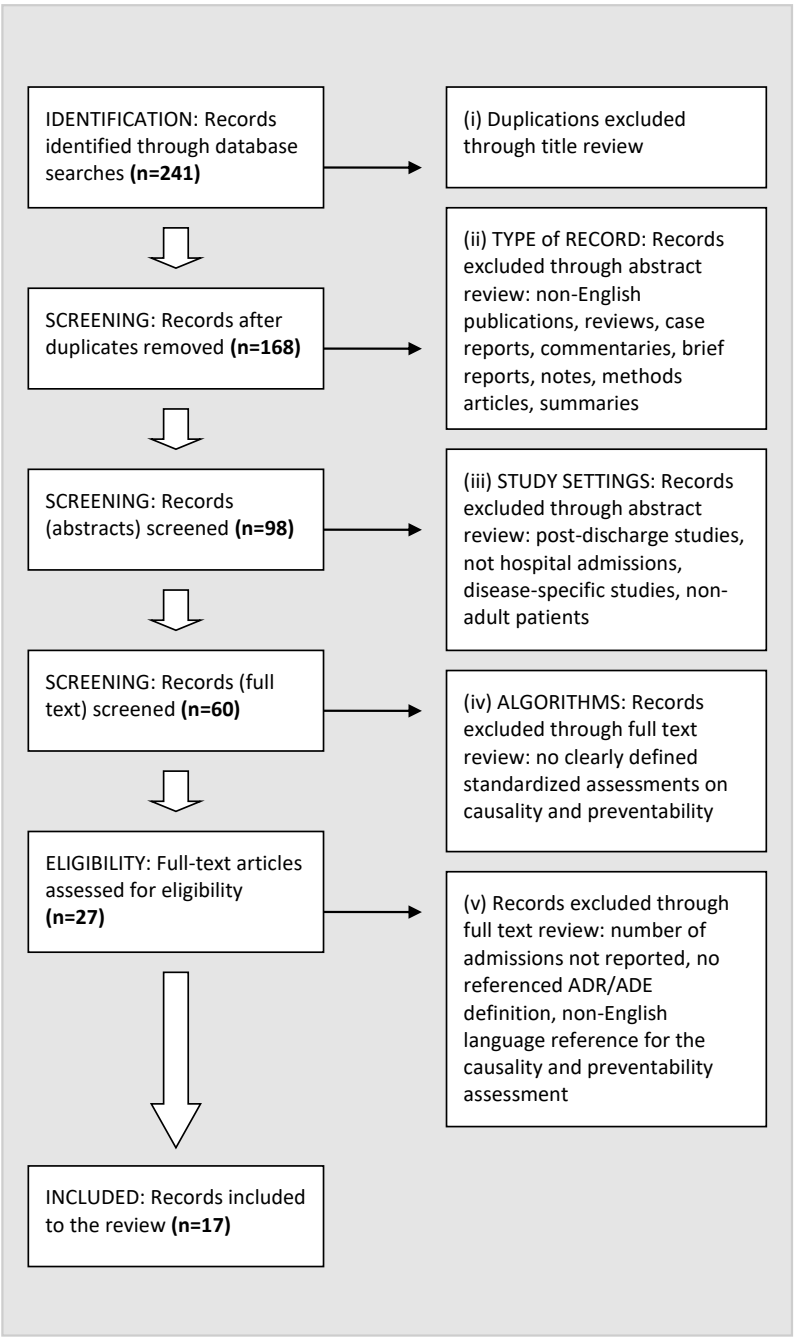
Publications presented only in abstracts, letters or editorials, studies evaluating methods, review studies, and non-English publications were excluded through title review. After data extraction by title review, disease-specific studies, post-discharge studies, studies without an adult patient population, and studies without hospital admissions were excluded through abstract review. One researcher performed the exclusion through title review (n=241) and abstract review (n=98). After that, two researchers reviewed the full text of the remaining publications (n=60) independently. Disagreements between reviewers were resolved by discussions.

Studies were retained if they reported both causality and preventability assessments based on a referenced algorithm scale. The following definition of an algorithm was adapted for this study [19]: standardized methods, which apply specific questions and associated scores to determine the likelihood of a cause-effect relationship between a drug and the ADR.

Two researchers independently assessed the remaining 27 publications for possible inclusion. Studies, which did not report the number of admissions, lacked a valid definition of ADR/ADE, or did not include an English language referenced algorithm for causality and preventability assessments were excluded.

Eligibility of the remaining 17 studies (Gholami et al. 1999, Chan et al. 2001, McDonnell and Jacobs 2002, Dormann et al. 2003, Dormann et al. 2004, Pirmohamed et al. 2004, al-Tajir et al. 2005, Davies et al. 2006, Patel et al. 2007, Rivkin 2007, Alexopoulou et al. 2008, Baniasadi et al. 2008, Franceschi et al. 2008, Hwang et al. 2008, Mehta et al. 2008, Davies et al. 2009, Calderón-Ospina et al. 2010) considered for the review was confirmed by unanimous agreement among three researchers. This systematic review conforms to the methodology and requirements in the PRISMA checklist (Moher et al. 2009).

The selected studies were fully reviewed, and the following data were studied: study design; type of the study units; the duration of the study; number of patients; ADR/ADE definition; predictability of the ADR/ADE; characteristics and prevalence of ADRs/ADEs; detection setting (on admission or during hospital stay); and the causality and preventability assessments of the ADRs/ADEs, including the results of these assessments.



ADR = adverse drug reaction; ADE = adverse drug event

Figure 2. Flow diagram of the data selection process.

2.1.2 Results of Stage I

Study characteristics

Of the seventeen studies included in Stage I systematic review, three were conducted in the United Kingdom (Pirmohamed et al. 2004, Davies et al. 2006 and 2009), and two each in Germany (Dormann et al. 2003 and 2004), Iran (Gholami et al. 1999, Baniasadi et al. 2008), and the United States (McDonnell and Jacobs 2002, Rivkin 2007) (Table 1). The remainder were conducted in the following countries (one each): Australia (Chan et al. 2001), Colombia (Calderón-Ospina et al. 2010), Greece (Alexopoulou et al. 2008), India (Patel et al. 2007), Italy (Franceschi et al. 2008), South Korea (Hwang et al. 2008), South Africa (Mehta et al. 2008) and United Arab Emirates (al-Tajir et al. 2005). Study settings varied substantially, as did the number of study patients (between 104 and 20, 166 patients), study periods (from 2 weeks to 18 months), and the number of study units (from one single ward to several wards of two hospitals) (Table 1). Except for two retrospective studies (McDonnell and Jacobs 2002, Hwang et al. 2008), all study designs were prospective, and most commonly prospective medication record reviews (11 out of 17 studies, Table 1). All studies in the final set were conducted between 1999-2010.

Definitions of ADR and ADE

Fourteen studies focused on ADRs, while the remaining three focused on ADEs. Ten studies described ADRs according to the original WHO definition (WHO 1969) (Table 2). Four studies used Edwards and Aronson's definition of an ADR (Edwards and Aronson 2010). Of the three remaining studies using definitions for ADE, one used the updated WHO definition (WHO 1999), one used the Bates et al. definition (Bates et al. 1995). One defined ADE by expanding WHO's ADR definition by including additional categories and definitions described earlier by Strand et al. (Strand et al. 1990) (Table 2).

Characteristics and prevalence of ADRs/ADEs

The seventeen studies reported a total of 4541 ADRs/ADEs (fourteen studies reported 3450 ADRs and three studies reported 1091 ADEs) in 68 101 patient cases, representing a 5.6% prevalence for ADRs and 18% prevalence for ADEs, with an overall 6.7% prevalence for either ADR or an ADE occurrence. In eight studies, predictability is estimated as Type A for predictable (or dose-dependent) and Type B for not predictable (or no clear dose-response relationship) (Rawlins and Thompson 1991) (Table 2).

Five of the studies reported 1030 ADRs/ADEs detected during the hospital stay among 5187 inpatients (19.9%; 7.7-31.3%). Nine studies reported 2164 ADRs/ADEs detected among 50 280 (4.3%; 0.8-31.7%) patients upon admission to the hospital (Table 3). Both ADRs/ADEs detected during the hospital stay, and those detected on admissions were reported by five studies comprising 1464 ADRs/ADEs among 13 954 (10.5%; 1.6-36.1%) patients (Table 3).

Table 1. Study settings of the included ADR/ADE studies, studies organized from newest to oldest (n=17).

Reference and country	Study design	Study units	Study duration	Patients (n)
ADR studies				
Calderon-Ospina et al. 2010 (Colombia)	prospective medication record review, descriptive cross-sectional	three wards (internal medicine, surgery, and obstetrics)	1 month	104
Davies et al. 2009 (UK)	prospective medical record review	12 wards (nine medical, three surgical)	6 months	3 695
Mehta et al. 2008 (South Africa)	prospective observational	two wards	3 months	665
Franceschi et al. 2008 (Italy)	prospective medical record review	one geriatric unit	14 months	1 756
Baniasadi et al. 2008 (Iran)	prospective review of spontaneous reports	seven various departments	12 months	6 840
Alexopoulou et al. 2008 (Greece)	prospective medical record review, interview	one department	6 months	548
Rivkin 2007 (USA)	prospective observational	one medical intensive care unit	19 weeks	281
Patel et al. 2007 (India)	prospective observational	one emergency department	6 weeks	6 899
Davies et al. 2006 (UK)	prospective medication record review	five wards	2 weeks	125
Pirmohamed et al. 2004 (UK)	prospective observational, medication record review	several departments of two hospitals	6 months	18 820
Dormann et al. 2004 (Germany)	cohort-based prospective medication record review	one internal medicine ward	18 months	844
Dormann et al. 2003 (Germany)	prospective medication record review	two wards	13 months	915
McDonnell and Jacobs 2002 (USA)	retrospective medical record review	one hospital	11 months	20 166
Gholami et al. 1999 (Iran)	prospective medication record review	two internal medicine departments	10 months	370
ADE studies				
Hwang et al. 2008 (South Korea)	retrospective medical record review	two intensive care units and five general wards	1 month	598
Al-Tajir et al. 2005 (United Arab Emirates)	prospective medication record review + spontaneous reporting	seven various units	12 months	5 235
Chan et al. 2001 (Australia)	prospective, cross-sectional, medication record review	acute medical units of one hospital	8 weeks	240

ADR = adverse drug reaction; ADE = adverse drug event

Table 2. Characteristics of ADRs/ADEs reported in each study, studies organized from newest to oldest (n= 17).

Reference	Definition of ADR/ADE	Prevalence of ADRs/ADEs n (%)	Detection setting for ADR/ADE	Predictable ADRs/ADEs
ADR studies				
Calderon-Ospina et al. 2010 (Colombia)	WHO	32 (30.8)	during hospital stay	88.5%
Davies et al. 2009 (UK)	Edwards and Aronson 2010	733 (19.8)	during hospital stay	94.1%
Mehta et al. 2008 (South Africa)	WHO	117 (17.6) total: 66 (10.1) on admission + 51 (7.7) during hospital stay	on admission and during hospital stay	84.8% on admission; 74.5% during hospital stay
Franceschi et al. 2008 (Italy)	Edwards and Aronson 2010	102 (5.8)	on admission	NA
Baniasadi et al. 2008 (Iran)	WHO	112 (1.6)	on admission and during hospital stay	NA
Alexopoulou et al. 2008 (Greece)	WHO	74 (13.5)	on admission	89.2%
Rivkin 2007 (USA)	WHO	21 (7.5)	on admission	NA
Patel et al. 2007 (India)	WHO	340 (4.9)	on admission	NA
Davies et al. 2006 (UK)	Edwards and Aronson 2010	27 (21.6)	during hospital stay	92.5%
Pirmohamed et al. 2004 (UK)	Edwards and Aronson 2010	1225 (6.5)	on admission	95.0%
Dormann et al. 2004 (Germany)	WHO	305 (36.1) total: 108 (12.8) on admission + 197 (23.3) during hospital stay	on admission and during hospital stay	NA
Dormann et al. 2003 (Germany)	WHO	102 (11.2)	on admission	NA
McDonnell and Jacobs 2002 (USA)	WHO	158 (0.8)	on admission	NA
Gholami et al. 1999 (Iran)	WHO	102 (33.2)	on admission and during hospital stay	96.1%
ADE studies				
Hwang et al. 2008 (South Korea)	Bates et al. 1995	187 (31.3)	during hospital stay	81.0%
Al-Tajir et al. 2005 (Unted Arab Emirates)	WHO	828 (15.8) total: 159 (3) on admission + 669 (12.8) during hospital stay	on admission and during hospital stay	NA
Chan et al. 2001 (Australia)	WHO and Strand et al.1990	76 (31.7)	on admission	NA

ADR = adverse drug reaction; ADE = adverse drug event

Table 3. Prevalence of ADRs/ADEs on admissions and during the patient's hospital stay (studies organized from newest to oldest).

Studies reporting ADRs/ADEs detected during the hospital stay	ADR/ ADE	number of patients	number of ADRs/ADEs	Prevalence of ADR/ADE (%)
Calderon-Ospina et al. 2010	ADR	104	32	30.8
Davies et al. 2009	ADR	3 695	733	19.8
Mehta et al. 2008	ADR	665	51	7.7
Davies et al. 2006	ADR	125	27	21.6
Hwang et al. 2008	ADE	598	187	31.3
Total		**5 187**	**1 030**	
Overall prevalence of ADRs/ADEs				**19.9**
Studies reporting ADRs/ADEs detected on admission	**ADR/ ADE**	**number of patient cases**	**number of ADRs/ADEs**	
Mehta et al. 2008	ADR	655	66	10.1
Franceschi et al. 2008	ADR	1756	102	5.8
Alexopoulou et al. 2008	ADR	548	74	13.5
Rivkin 2007	ADR	281	21	7.5
Patel et al. 2007	ADR	6 899	340	4.9
Pirmohamed et al. 2004	ADR	18 820	1 225	6.5
Dormann et al. 2003	ADR	915	102	11.2
McDonnell and Jacobs 2002	ADR	20 166	158	0.8
Chan et al. 2001	ADE	240	76	31.7
Total		**50 280**	**2 164**	
Overall prevalence of ADRs/ADEs				**4.3**
Studies reporting combined results for ADRs/ADEs both detected on admission and during the hospital stay	**ADR/ ADE**	**number of patient cases**	**number of ADRs/ADEs**	
Mehta et al. 2008	ADR	665	117	17.6
Baniasadi et al. 2008	ADR	6 840	112	1.6
Dormann et al. 2004	ADR	844	305	36.1
Gholami et al. 1999	ADR	370	102	27.6
Al-Tajir et al. 2005	ADE	5 235	828	15.8
Total		**13 954**	**1 464**	
Overall prevalence of ADRs/ADEs				**10.5**

ADR = adverse drug reaction; ADE = adverse drug event

Results of the causality assessments

There were mainly three different algorithm methods used to estimate causality of ADRs/ADEs: Naranjo's scale (Naranjo et al. 1981) in fourteen studies, method of WHO (WHO-UMC) in two studies, and a modification of Hallas' method (Hallas et al. 1990) in one study (Table 4). In one study (al-Tahir et al. 2005), an additional assessment for drug interactions (Hansen and Horn 2000) was combined with Naranjo's scale (Naranjo et al. 1981). In one study (Pirmohamed et al. 2004), besides Naranjo's scale, an additional causality assessment according to Jones (Jones 1982) was used, and the results from these two different causality assessments were reported separately (Table 4).

Table 4. Assessments for causality and preventability (studies organized from newest to oldest).

Studies	Assessment method for causality (C) and preventability (P)	Causality	Preventability (Avoidability)
Calderon-Ospina et al. 2010 (Colombia)	C: WHO-UMC; P: Schumock and Thornton	definite: 7.7%; likely: 38.5%; possible: 53.8%	preventable: 50.0%
Davies et al. 2009 (UK)	C: Naranjo; P: Hallas	definite: 3.1%; probable: 66.5%; possible: 30.4%	definite: 6.4%; possible: 46.9%; unavoidable: 46.7%
Mehta et al. 2008 (South Africa)	C: WHO-UMC; P: Schumock and Thornton	hospital-acquired ADRs: definite: 17.6%, probable: 54.9%; possible: 27.5%, community-acquired ADRs: definite: 18.2%; probable: 40.9%; possible: 40.9%	hospital-acquired: preventable: 33.3%; community-acquired: preventable: 53.0%
Franceschi et al. 2008 (Italy)	C: Naranjo; P: Hallas	definite: 6.8%; probable: 91.2%; possible: 2.0%	definite: 45.1%; possible: 31.4%; unavoidable: 18.6%; unclassified: 4.9%
Baniasadi et al. 2008 (Iran)	C: Naranjo; P: Schumock and Thornton	highly probable: 4.6%; probable: 68.5%; possible: 26.9%	preventable: 22.3%
Alexopoulou et al. 2008 (Greece)	C: Naranjo; P: Hallas	definite or probable: 74.3%; possible: 25.7%	preventable: 18.6% possibly preventable: 24.3%; not preventable: 57.1%
Rivkin 2007 (USA)	C: Naranjo P: Schumock and Thornton	definite: 4.8%; probable: 81.0%; possible: 14.2%	preventable: 85.7%
Patel et al. 2007 (India)	C: Naranjo; P: Hallas	definite: 3.8%; probable: 85.9%; possible: 10.3%	definite: 10.2%; possible: 49.4%; unavoidable: 40.4%
Davies et al. 2006 (UK)	C: Naranjo; P: Hallas	definite: 4.0%; probable: 33.0%; possible: 63.0 %	definite: 11.0%; possible: 48.0%; unavoidable: 41.0%
Pirmohamed et al. 2004 (UK)	C: Naranjo + Jones; P: Hallas	(Naranjo): definite: 1.9%; probable: 68.7%; possible: 29.4%/ (Jones): highly probable:0.5%; probable: 61.4%; possible: 38.1%	definitely avoidable: 9.0%; possibly avoidable: 63.0%; unavoidable: 28.0%
Dormann et al. 2004 (Germany)	C: Naranjo; P: Schumock and Thornton	both hospital and community-acquired ADRs: definite: 6.2%; probable: 57.4%; possible: 35.7%	both hospital and community-acquired: preventable: 44.3%
Dormann et al. 2003 (Germany)	C: Naranjo; P: Schumock and Thornton	definite: 10.8%; probable: 43.1%; possible: 46.1%	preventable: 41.2%
McDonnell and Jacobs 2002 (USA)	C: Naranjo; P: Schumock and Thornton	probable or highly probable: 97.5 %; possible or doubtful: 2.5%	preventable: 60.8%
Hwang et al. 2008 (South Korea)	C: Naranjo; P: Schumock and Thornton	definite: 3.0%; probable: 43.0%; possible: 53.0%; doubtful 1.0%	preventable: 16.0% nonpreventable: 84.0%
Al-Tajir et al. 2005 (United Arab Emirates)	C: Naranjo + Hansten and Horn (drug interactions) P: Schumock and Thornton	Definite: 1.1%; probable: 55.8%-53.5%; possible: 41.4%- 44.5%; doubtful: 1.6%- 0.8%	Preventable: 14.6%-18.2%
Chan et al. 2001 (Australia)	C: Hallas; P: Hallas	definite: 20.1%; probable: 41.4%; possible: 31.4%; possible/possible: 7.1%	Definitely preventable: 53.4%; possibly preventable: 23.3%; not preventable: 23.3%.

Since different causality rating terms were used in the studies, we re-grouped the reported rating terms into three main categories i: definite, certain, or highly probable; ii: probable or likely; iii: possible. Of the seventeen studies, two (McDonnell and Jacobs 2002, Alexopoulou et al. 2008) were excluded because they reported combined results from causality ratings and could not be grouped in the taxonomy above. The remaining fifteen studies (4309 ADRs/ADEs among 47 387 patients) reported definite, certain or highly probable causality between 1.1%-20.0% (median 4.8%; mean value: 7.1%); and probable or likely causality between 33.0%-91.2% (median: 57.4%; mean value: 58.3%); and possible causality between 2.0%-63.0% (median: 33.7%; mean value: 33.4%). Of the seventeen studies, causality rates: definite/certain/highly probable or probable/likely were reported between 37%-98% (median: 64.9%; mean value: 67.8%).

Causality for ADRs/ADEs on hospital admissions was assessed in nine studies and was rated as definite/certain/highly probable or probable/likely between 53.9%-98.0% (median: 74.3%; mean value: 75.9%). Causality for ADRs/ADEs during the hospital stay was assessed by five studies and was rated as definite/certain/highly probable or probable/likely between 37.0%-72.5% (median: 46.2%; mean value: 54.3%) (Table 4).

Results of the preventability assessments

In the seventeen studies, Schumock and Thornton (Schumock and Thornton 1992) and Hallas (Hallas et al. 1990) were the two most commonly used preventability scales (Table 4). Schumock and Thornton was used in ten studies, while Hallas was used in seven studies. The reported preventability rating terms were then re-grouped into categories for the analysis: *i: definite or preventable/avoidable; ii: possible or possibly; iii: unpreventable/unavoidable.* Preventability reported as *definite* or *preventable* in all seventeen studies ranged between 6.4%-85.7% (median: 41.2%; mean value: 34.9%). Seven studies reported *possible* preventability between 23.3%-63.0% (median: 46.9%; mean value: 40.9%); and nine studies reported *unpreventable/unavoidable* between 18.6%-84.0% (median: 40.4%; mean value: 46.5%). Preventability for ADRs/ADEs on admissions was assessed in nine studies and was rated as *definite* or *preventable/avoidable* between 9.0%-85.7% (median: 45.1%; mean value: 41.9%). Five studies assessed preventable ADRs/ADEs during the hospital stay and rated them as *definite* or *preventable/avoidable* between 6.4%-50.0% (median: 16.0%; mean value: 23.3%).

2.2 Stage II: A literature review of the studies between 2011-2020 (using the most common algorithms)

2.2.1 Search strategy and data extraction

In the second stage of the review, research articles were searched from January 2011 to December 2020 using the same terms used in Stage I systematic review 1990-2010 (Review I). MeSH terms were also used, where appropriate, in combination with search terms. In the literature review 2011-2020 (Review II), only the studies that used the Naranjo scale (Naranjo et al. 1981) for the causality assessment and the Schumock and Thornton criteria (Schumock and Thornton 1992) for the preventability assessment were included. This decision was made because, in the systematic review 1990-2010, these assessments were applied most commonly in the selected studies (the Naranjo probability scale: 14/17; the Schumock and Thornton criteria: 10/17) (Table 4). Another reason for this was also to achieve better comparability among the selected studies. Selected studies were thoroughly reviewed, and the following data were studied: the settings and the duration of the study; the number of ADRs/ADEs; the results of the causality and preventability assessments and the most commonly related drugs in the ADRs/ADEs.

2.2.2 The Naranjo scale and the Schumock and Thornton criteria

The Naranjo probability scale (Naranjo et al. 1981) for the causality assessment includes ten questions that are answered “Yes,” “No,” or “Do not know.” The point values (-1, 0, +1, or +2) are assigned to each answer resulting in total scores ranging from -4 to +13 (Table 5). The ADR/ADE is considered definite if the score is nine or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less (Naranjo et al. 1981).

The original Schumock and Thornton criteria, first introduced in 1992 (Schumock and Thornton 1992), includes seven questions (assessed by yes or no answers); answer of yes to one or more of the questions indicates that the harm was preventable (Table 6).

Some studies have modified this criterion by adding to the original version two additional questions and grouping the questions into the three parts named “definitely preventable”, “probably preventable” and “non-preventable” (Angamo et al. 2017, Lo Giudice et al. 2019). In this modified version, part A consists of five questions, while part B has four questions. All the answers are categorized as “Yes” or “No.” The ADR/ADE is assessed as “definitely preventable” if the answer is “yes” to one or more questions in part A. If responses are all negative, then assessment continues to part B, where the ADR/ADE is assessed as “probably preventable” if the answer is “yes” to one or more questions in part B. If responses were all negative, the ADRs/ADE is assessed non-preventable, shown in part C (Table 7).

Table 5. The Naranjo probability scale (Naranjo et al. 1981).

Question	Yes	No	Do not know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 6. The original Schumock and Thornton criteria (Schumock and Thornton 1992) for assessing the preventability of an ADR (ADE).

Question: An answer of yes to one or more of the following questions indicates that the harm was preventable	**Answer:** Yes/No
1. Was the drug involved in the adverse drug reaction not considered appropriate for the patient's clinical condition?	
2. Was the dose, route, and frequency of administration not appropriate for the patient's age, weight, and disease state?	
3. Was required therapeutic drug monitoring or other necessary laboratory testing not performed?	
4. Was there a history of allergy or previous reactions to the drug?	
5. Was a drug interaction involved in the reaction?	
6. Was a toxic serum drug level documented?	
7. Was poor compliance involved in the reaction?	

Table 7. The modified version of the Schumock and Thornton criteria (Angamo et al. 2017, Lo Giudice et al. 2019).

A: Definitely preventable
1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5. Was there a known treatment for the adverse drug reaction? *
B: Probably preventable
6. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventative measures not prescribed or administered to the patient? *
C: Not preventable
If all the above criteria are not fulfilled

** Additional question in the modified version.*

2.2.3 The results of Stage II

The search for the studies which used the Naranjo scale (Naranjo et al. 1981) and the Schumock and Thornton criteria (Schumock and Thornton 1992) resulted in 39 publications after the exclusion of publications presented only in abstracts, letters or editorials, studies evaluating methods, review studies, and non-English papers. Of the 39 results, studies with the settings of specific drugs and non-adult patients were further excluded, and seven studies were included to be reviewed (Table 8). Four out of seven studies (three studies from India and one from South Korea) used spontaneous reporting data, while the remaining three (from Australia, Colombia, and Ethiopia) were prospective studies. The duration of the studies varied between four months to 5.5 years. Studies analyzed a total of 1173 ADR/ADE cases. Causality was assessed certain/definite (1.0%-26.1%), probable/possible (32.0%-90.0%). The Preventability of the ADRs/ADEs varied between 0.5%-92.2%. Studies reported variable drugs or therapeutic drug groups responsible for the ADRs/ADEs (Table 8).

Table 8. Study settings and findings of the selected studies (n=7) using the Naranjo's scale (Naranjo et al. 1982) for the causality assessment and the Schumock and Thornton's (Schumock and Thornton 1992) criteria for the preventability assessment between 2011-2020 (studies organized from newest to oldest).

Study	The settings and the duration of the study	Number of ADRs/ADEs	Assessment of causality and preventability and most commonly related drugs
Angamo et al. 2017, Ethiopia	ADR-related hospitalizations reviewed for 16 months in patients admitted to medical wards	103	- Definite: 26.1%; probable: 73.9%. - Definitely or probably preventable 89.0%. - Antitubercular agents, antivirals and diuretics.
Rojas-Velandia et al. 2017, Colombia	Prospective study in patients admitted to the ICU, 4 months	108	- Definite: 0.9%; probable: 32.4%; possible: 42.5%. - Preventable 44.0%. - Acetylsalicylic acid and losartan.
Prajapati et al. 2016, India	Spontaneous reporting in a tertiary care teaching hospital, 5.5 years	375	- Certain: 0.3%; probable: 66.9%; possible: 32.5%; unclassified: 0.3%. - Preventable: 0.5%. - Antitubercular and antiretroviral agents.
Nair et al. 2016, Australia	Prospective study in patients aged ≥65 years admitted to two hospitals, 12 months	115	- Definite: 5.8%; probable: 69.3%; possible: 24.9%. - Preventable: 92.2%. - Antihypertensives and anticholinergics.
Ponnusankar et al. 2015, India	Spontaneous reporting in secondary care hospital, 1 year	47	- Definite: 4.0%; probable: 90.0%; possible: 6.0%. - Preventable: 23.0%. - Antibiotics.
Ryu et al. 2015, South Korea	Spontaneous reporting by an in-hospital pharmacovigilance center, two years	328	- Certain 3.0%, probable 60.0%; possible: 37.0%. - Preventable 10.0%. - Neurological drugs, such as tramadol, pethidine, and fentanyl, followed by antibiotics, including cephalosporin and vancomycin.
Patel et al. 2015, India	Spontaneous reporting in a psychiatry department, 3 years	97	- Definite: 1.0%; probable: 56.0%; possible: 43.0%. - Preventable: 38.0%. - Antipsychotics.

ADR = adverse drug reaction; ADE = adverse drug event.

2.3 Strength and limitations

This two-staged review (review I: 1990-2010 and review II: 2011-2020) aimed to evaluate the cause-effect relationship between a drug and an adverse event and the preventability of the ADRs/ADEs with relevant algorithms. Because of the wide variety of assessment methods used in the selected studies in the review I (1990-2010), it was challenging to compare the assessment results. Because of this reason, in review II (2011-2020), the aim was to identify more similar studies. Therefore, the protocol of review II was aimed to identify studies that used Naranjo's scale for causality assessment and Schumock and Thornton criteria for the preventability assessment. These assessment methods were selected because the review I showed that they were the most common ones in the studies.

The main limitation of this thesis' review arises from the challenge of combining results from a wide variety of study settings and designs. Secondly, only English language publications were considered, and studies that did not have English language references for the assessment methods were also excluded. Thus, some relevant publications may have been omitted. Thirdly, only seven studies that used Naranjo's scale and Schumock and Thornton criteria were identified in review II. By doing so, other possibly relevant studies using different methods have been omitted. However, Pubmed search in October 2021 shows that Naranjo's scale and Schumock and Thornton criteria were still frequently used algorithm-based assessment methods for the assessment of the causality and preventability of the ADRs/ADEs between the years 2011-2020: Naranjo's scale was used in a total of 808 and Schumock and Thornton criteria was used in a total of 57 English language journal research articles. Respectively other algorithm-based methods, WHO-UMC (72 results) for the causality assessment and Hallas' assessment (18 results together for causality or preventability assessments), were preferred less frequently.

Wolfe et al. reported a comprehensive overview of reviews (i.e., a systematic review of systematic reviews) to determine the incidence of preventable ADRs experienced by inpatients and explored 13 systematic reviews, including 37 studies. Selected studies used various causality and preventability methods, algorithms, and other methods. (Wolfe et al. 2018). Naranjo's scale was the most frequently used causality assessment method (8 out of 37; 22%), and Schumock and Thornton criteria (and adaptations) was also the most commonly used preventability assessment (6 out of 37; 16%). As a side note, in that study (Wolfe et al. 2018), assessment methods were not used or reported in many of the selected studies – methods for causality assessment were not reported in 20/37 studies (54%), and for the method for preventability assessment were not reported in 6/37 studies (16%).

A wide variety of different health care systems in previous studies can also be counted as limitations. Besides these limitations, this two-staged review has found results supporting earlier findings regarding the considerably high prevalence of the causality and the preventability of the ADRs/ADEs detected in different health care settings (Bates et al. 1995, Lazarou et al. 1998, Hakkarainen et al. 2012a, Wolfe et al. 2018, Jennings et al. 2020, Insani et al. 2021).

2.4 Summary of key findings and implications for future research

A cause-effect relationship between an adverse event and the suspected drug was definite or probable/likely in most cases. The prevalence of ADRs/ADEs detected during the hospital stay among inpatients was higher than that detected on admissions. However, ADRs/ADEs detected on admission were twice as likely to be preventable as those detected during a patient's hospital stay. Overall, one-third of the ADRs/ADEs were likely preventable; however, the preventability results varied between the studies between 0.5-92.2%.

There is a substantial opportunity for improvement in medication practices that would reduce medication-related harm to patients. Inadequate therapeutic monitoring and IP should be the two critical issues for improvement in hospitals. As most of the studies included in the reviews I and II suggest, high-risk patients – especially older patients with multiple diseases using multiple concurrent medications - must be identified early and routinely screened. This review showed that high-risk medications, i.e., opiates, anticoagulants, antibiotics, NSAIDs, cardiovascular agents, and BZD, were frequently involved in preventable ADEs, i.e., GI bleeding, hepatotoxicity, heart failure, and falls. A comprehensive review study found precisely the same medicines (Wolfe et al. 2018). It noted that substantial reduction in errors in the medication process leading to preventable ADRs/ADEs may not occur without multi-component interventions, including institutional, cultural change (Wolfe et al. 2018).

An earlier review (Lewis et al. 2009) showed that prescribing errors occurred in 7% of medication orders, 2% of patient days, and 50% hospital admissions. Another study observed that 19% of medication administrations had errors, including wrong time, omission, or wrong dose, based on broad research in various health care facilities (Barker et al. 2002). A previous systematic review found that clinical pharmacists were more efficient than other clinicians were in identifying ADEs (Phansalkar et al. 2007). Many earlier studies have reported improvements - such as a reduction in ADE occurrence, length of stay, hospitalizations, morbidity, and mortality rates - resulting from pharmacists' interventions, for example medication reviews, medication reconciliation, and drug information (Bond and Raehl 2006, Kaboli et al. 2006, Terceros et al. 2007). Medication reviews with pharmacist participation have been suggested to reduce preventable IP (Rankin et al. 2018).

To identify and reduce preventable drug-related harm among hospital patients, it is crucial to clearly state which specific medication practices are responsible for the ADEs in routine practice. In future studies, the possible cause-effect relationship between an observed adverse event and a ME (wrong medication, wrong dose, wrong administration route, wrong administration time, and wrong patient) should also be well established. Further research is needed for implementing effective ADE prevention strategies, particularly in prescribing medications and monitoring their use. From the risk management aspect, special attention should be paid to older patients and to such health care units where the workload is heavy and medication process is complex, such as emergency wards.

3 AIMS OF THE STUDY

This doctoral thesis aimed at developing safe medication practices within a regional health care district. The practices included in this thesis were selected from three different operational levels of the system: 1) organizational level; 2) health care unit and clinical practice level; 3) patient care and medication use level. The thesis had the following three objectives:

I. To develop and validate a medication safety self-assessment tool (MSSA) to be used in secondary care hospital wards (*Study I: organizational level);*

II. To use clinical pharmacist-conducted collaborative medication reviews (CMRs) in an emergency department (ED) short-term ward to identify inappropriate prescribing (IP) in pre-admission medications; *(Study II: health care unit and clinical practice level);*

III. To investigate how well older people are aware of the potential risks of benzodiazepines and related drugs (BZD) they are taking and whether the risk awareness changed between the years 2004 and 2015 *(Study III: patient care and medication use level).*

This doctoral thesis applied a systems approach to medication risk management based on the Theory of Human Error as a theoretical framework (Reason 2000).

4 STUDY DESIGN AND METHODS

The health care district in the Satakunta Region

The studies I-III were conducted within the same health care district in the Satakunta Region located on the West Coast of Finland, with a population of 217 000 (Satasairaala, Satakunnan sairaanhoitopiirin kuntayhtymä, Satakunta health care district 2021). In Finland, health care services are divided into primary health care and specialized medical care, i.e., secondary care (Ministry of Social Affairs and Health of Finland, MSAH 2021a). Primary health care services are provided at municipal health centers and primary care hospitals. Specialized medical care is mainly provided at secondary care hospitals called central hospitals (Ministry of Social Affairs and Health of Finland, MSAH 2021a).

Municipalities form hospital districts that are responsible for providing specialized medical care in their area (Ministry of Social Affairs and Health of Finland, MSAH 2021a). Finland is divided into 21 hospital districts. Each district is responsible for the provision of municipal secondary care services. Each municipality must be a member of one hospital district. Hospital districts are financed and managed by the member municipalities (Ministry of Social Affairs and Health of Finland, MSAH 2021a). In addition, each hospital district belongs to one of the five catchment areas for highly specialized medical care, which are formed around the University Hospitals of Helsinki, Turku, Tampere, Oulu, and Kuopio. The most demanding tertiary care is provided in these hospitals (Ministry of Social Affairs and Health of Finland, MSAH 2021a). Municipalities or joint municipal authorities may also procure health care services from private service providers i.e. occupational health care services. Employers are responsible for preventive health care of their employees (Ministry of Social Affairs and Health of Finland, MSAH 2021a). To receive non-emergency specialized medical care, the patient must have a referral issued by a general practitioner at the primary care health center or an occupational health physician (Ministry of Social Affairs and Health of Finland, MSAH 2021a).

Municipalities of the Satakunta Region form the regional Satakunta health care district. They are responsible for the primary health care services and providing specialized medical care for the residents in their area. In the Satakunta Region, Satasairaala Hospital is responsible for specialist care and 16 municipal health centers for primary care (Satasairaala, Satakunnan sairaanhoitopiirin kuntayhtymä, Satakunta health care district 2021).

Summary of the study designs

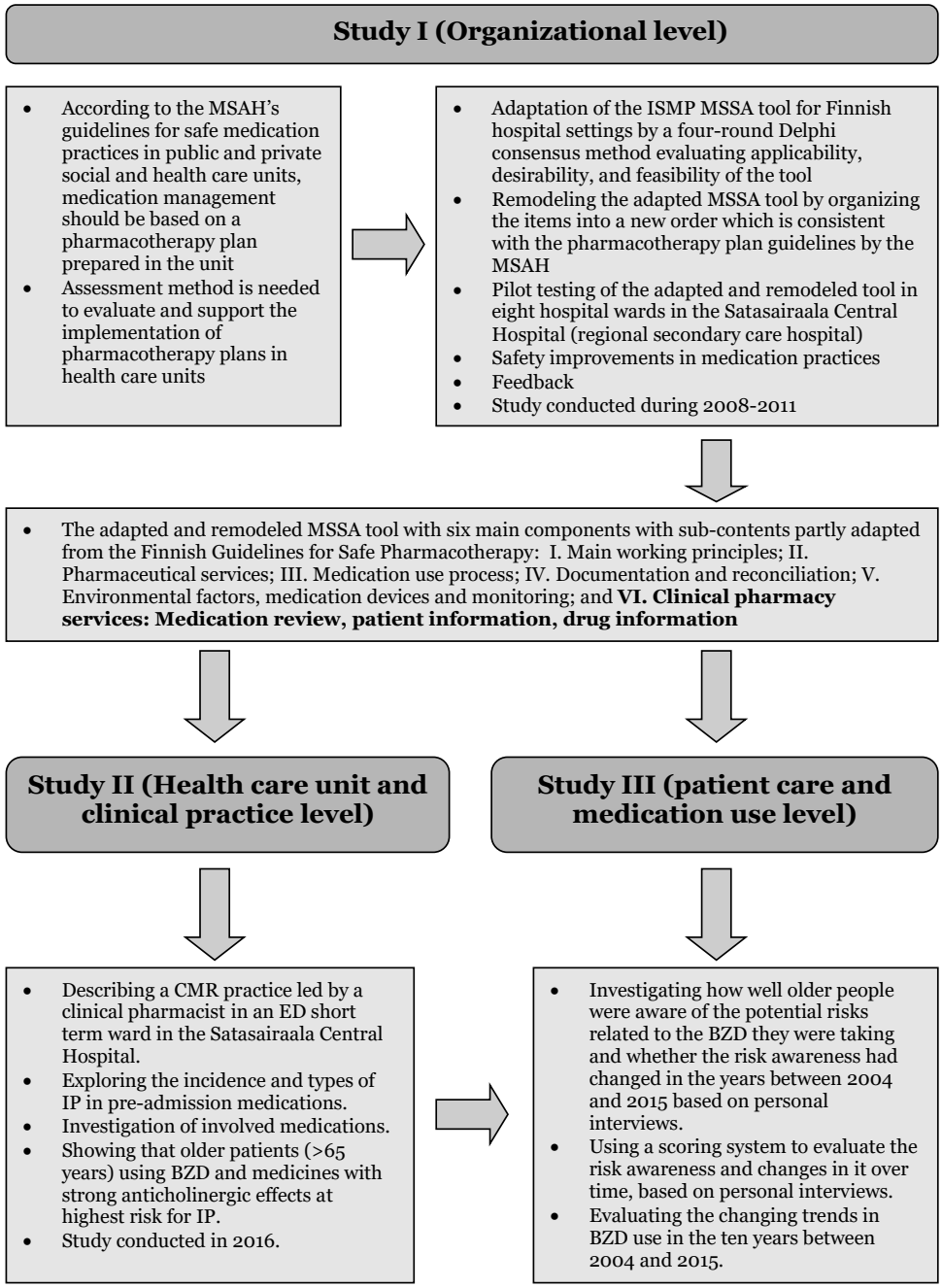
This doctoral thesis includes three empirical studies, each focusing on a different operational level of practice. The selected practices were from the following operational levels: 1) organizational level; 2) health care unit and clinical practice level; 3) patient care and medication use level (Figure 3).

In the first study (Study I), the MSSA tool for hospitals of the Institute for Safe Medication Practices (ISMP) was adopted and then remodeled for Finnish hospital settings by the Delphi consensus method. The developed tool was pilot tested in

various hospital wards of one regional secondary care hospital (Satasairaala Central Hospital) in the same study. Improvements for safe medication practices were documented. This multi-phased study was carried out between the years 2008-2011.

Study II has its origins in Study I. One of the six main components of the adapted and remodeled MSSA tool was clinical pharmacy services with sub-contents: medication review, patient information, and drug information. At the time of the first study, there were no ward-based clinical pharmacy services available in the study hospital. Therefore, clinical pharmacy services were selected as an area for development in the hospital region. Of the clinical pharmacy services, the development focused on collaborative medication reviews led by a clinical pharmacist in an ED in the Satasairaala Central Hospital. In that 5-month prospective study in 2016, the incidence and types of IP in pre-admission medications were explored, and involved medications were documented.

Study II indicated that BZD were one of the most frequently involved medications in IP in pre-admission medications, particularly in older (>65 years) ED patients. Consequently, in Study III, the risk awareness of older BZD users was investigated using two cross-sectional patient data sets collected from a public primary care hospital in the City of Pori in one-month periods in the years 2004 and 2015. Study patients were interviewed to determine how well they were aware of the potential risks of the BZD they were taking and whether the risk awareness had changed in the years between the two study periods.



MSAH = Ministry of Social Affairs and Health (Finland); ISMP = Institute for Safe Medication Practices, USA; MSSA = Medication Safety Self-Assessment; CMR = Collaborative medication reviews; ED = Emergency Department; IP = Inappropriate prescribing; BZD = Benzodiazepines and related drugs.

Figure 3. Outline of the studies (Studies I-III).

4.1 Adapting and remodeling the US Institute for Safe Medication Practices' Medication Safety Self-Assessment Tool for Hospitals (Study I)

4.1.1 Study design and methods

According to the inventory made, few comprehensive and practical tools exist that guide assessment of safe medication practices on hospital wards. The most comprehensive of the tools found was the Medication Safety Self-assessment (MSSA) tool for hospitals by the US Institute for Safe Medication Practices (ISMP). The US ISMP MSSA tool contains items that address the safe use of medications, system improvements, and safeguards based on the analysis of MEs reported to the ISMP Medication Errors Reporting Program (ISMP 2011). The US MSSA tool for hospitals has been adapted for use in other countries, for example Canada, Australia, and Spain (Greenall et al. 2005, New South Wales Therapeutic Advisory Group, Clinical Excellence Commission, Australia 2002; ISMP Spain 2015). The tool was released first in 2000, updated in 2004, and later in 2011 (ISMP 2011). However, there is no previous research reporting the US ISMP's MSSA tool's adaptation process in other countries, taking into account differences in health care systems.

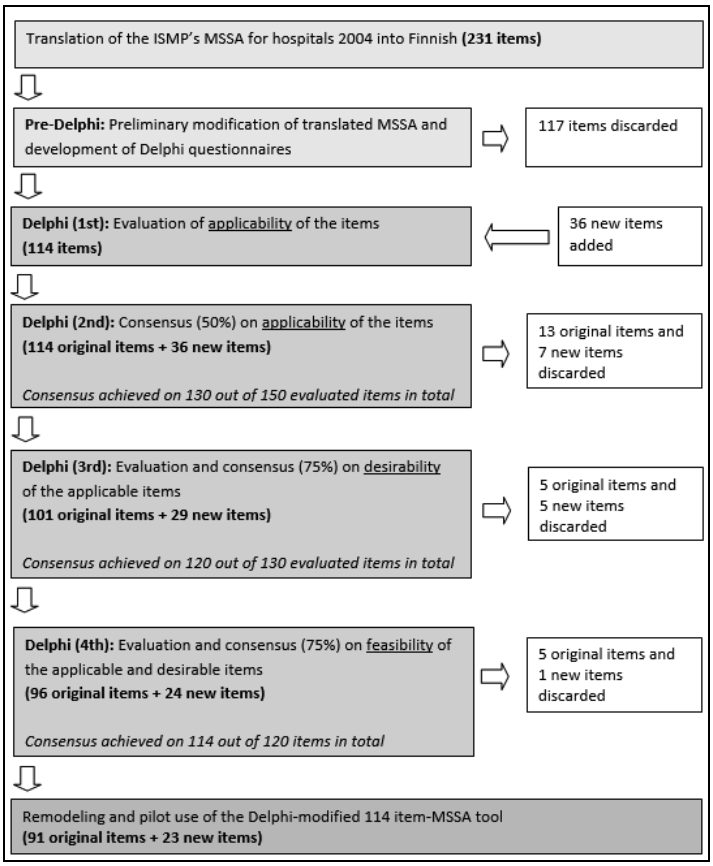
The US ISMP's MSSA tool for hospitals 2004 (ISMP 2004) was first adapted for Finnish hospital settings by a four-round (applicability, desirability, and feasibility were evaluated) Delphi consensus method (14 panelists), and then remodeled by organizing the items into a new order which is consistent with the order of the ward-based pharmacotherapy plan recommended by the MSAH (MSAH 2006). The adapted and remodeled tool was pilot tested in eight central hospital wards at Satasairaala Central Hospital (formerly Satakunta Central Hospital). The overall study design is shown in Figure 4.

The Delphi is a method for structuring a group communication process so that the process is effective in allowing a group of individuals to deal with a complex problem (Linstone and Turoff 2002). The Delphi method is an iterative multistage process for deriving consensus among separate expert panels (Hasson et al. 2000). The Delphi method has been used in many studies to obtain consensus on different types of health care problems, for example by developing medication risk management tools and guidelines (Puumalainen et al. 2005, Teinilä et al. 2012, Dimitrow et al. 2014).

4.1.2 Pre-Delphi modification and Delphi rounds

The original US MSSA tool for hospitals 2014 (231 items) (ISMP 2004) was translated into Finnish and then preliminarily modified by the research team members before sending it to the Delphi panelists. The research team coordinating

the Delphi study consisted of five licensed pharmacists in Finland and having clinical and academic experience. An item was considered unsuitable and discarded if it was not regarded as applicable to the Finnish health care and hospital settings because of the Finnish legislation, inapplicable information technologies, or type of practices at that time or in near future. In addition, since the original MSSA tool for hospitals was designed to assess the implementation of practices in an entire health care organization (hospital), some items of the MSSA were not applicable to be used in assessing an individual hospital ward.



ISMP = Institute for Safe Medication Practices; MSSA = Medication Safety Self-Assessment.

Figure 4. Study design (Study I).

The Delphi method (Linstone and Turoff 2002) was used for further modification of the tool. The criterion for selecting and inviting expert panelists for the Delphi rounds was that they had extensive clinical experience in pharmacotherapy in hospitals. Selected experts were approached by an invitation letter via email introducing the study protocol and asking their willingness to contribute to the study as an expert panelist. Instructions and the questionnaire in Excel format were sent

to the panelists for each Delphi round via email. Also, responses were collected, and reminders were sent by email.

Four Delphi consensus rounds were performed (Figure 4). In the first Delphi round, panelists were asked (1) to evaluate the applicability of each item by using a three-point scale (applicable; not applicable; and need for clarification), also (2) to comment on or revise each item according to their opinion, or suggest a new item if necessary. Items that needed clarification at least from one panelist were revised for clarity to all panelists. The applicability of these items was assessed one more time at the second Delphi round. If more than half of the panelists considered an item not applicable, it was assessed again at the second Delphi round. If more than half of the panelists considered an item applicable in the first Delphi panel, it was moved directly to the third round for the desirability assessment. In the second Delphi round, panelists were asked to evaluate the applicability of each item by using a three-point scale (applicable; not applicable; and no opinion). Items were accepted for the third round only if considered applicable by more than half of the panelists. In the third round, panelists were asked to evaluate the desirability (effectiveness or benefits) (Linstone and Turoff 2002) of each remaining item (consensus rate: 75%) by using a three-point scale (desirable/somewhat desirable; no opinion; not desirable/somewhat not desirable). The panelists were again asked to comment on or revise each item according to their opinion, if necessary. In the final, fourth, round consensus for feasibility (practicality) (Linstone and Turoff 2002) was obtained for the remaining items (consensus rate: 75%). A three-point scale (feasible/somewhat feasible; no opinion; not feasible/somewhat not feasible) was used. Items on which consensus (75%) was not reached were discarded (Figure 4).

4.1.3 Remodeling the Delphi-modified Medication Safety Self-Assessment tool and pilot use

The Delphi-modified MSSA tool for hospitals was remodeled by organizing the final items into a new order consistent with the recommendation by the MSAH to establish ward-based pharmacotherapy plans in hospitals (MSAH 2006).

The Delphi-modified and remodeled MSSA tool was then pilot tested in various wards in Satasairaala Central Hospital (formerly Satakunta Central Hospital). All the main medical wards of the hospital were selected for the pilot. The nurse managers of the selected wards were contacted via email to ask their willingness to contribute to the pilot. The MSSA tool was introduced to the nurse managers of the selected wards in a meeting. The nurse managers conducted the self-assessment in each ward by estimating how well each of the items of the MSSA tool was implemented in the pilot ward's pharmacotherapy plan.

A five-point rating scale: fully; partly; poorly implemented; not implemented or not applicable was applied to the self-assessment. The assessment results were then discussed with each nurse manager of the pilot ward, and reports were prepared based on each assessment result. In each report, medication practices inadequately

implemented were identified as high-risk areas in the medication management process. Nurse managers of the pilot wards were asked to respond to these reports in one month by addressing the implemented improvements based on the MSSA assessment results.

Lastly, the nurse managers of the pilot wards were interviewed to get feedback from the MSSA tool and its use in practice. It was an open group interview; opinions of the nurse managers of the pilot wards were asked on the comprehensiveness and usefulness of the tool and the amount of time consumed for the self-assessment. The nurse managers of the pilot wards were also asked what would be the most suitable frequency for conducting the MSSA and under whose responsibility the MSSA practice should be coordinated in the future. The responses provided during the interview were collected as hand-written notes. They were analyzed using content analysis.

4.2 Collaborative medication reviews to identify inappropriate prescribing in pre-admission medications at emergency department short-term ward (Study II)

4.2.1 Evolution of collaborative medication review practices in Finland

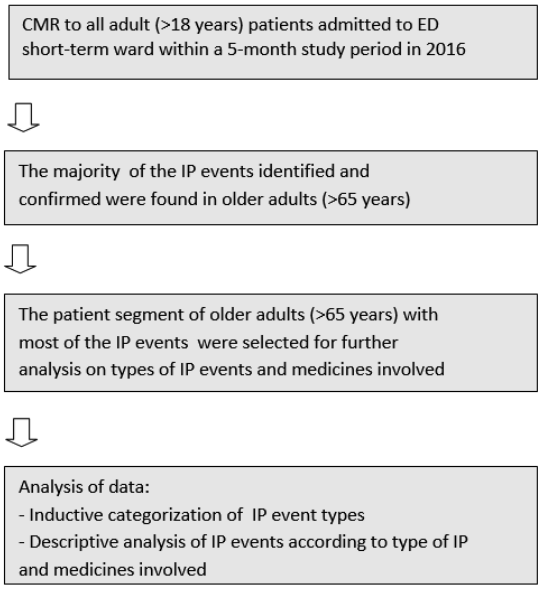
In Finland, collaborative medication reviews (CMR) are a relatively new practice. The first CMR procedures were developed in 2005 as part of a long-term continuing education providing accredited comprehensive CMR competence for practicing pharmacists (Leikola et al. 2012, Kiiski et al. 2019). Therefore, the development of CMR practices in Finland began from comprehensive reviews, which then extended to less comprehensive procedures such as medication list reviews (i.e., prescription reviews) and various medication review procedures (Leikola et al. 2009, Leikola et al. 2012, Kiiski et al. 2019). After 2005, CMRs have become more common in Finnish hospitals, although the progress has been relatively slow (Kiiski et al. 2019, Schepel et al. 2019). An inventory conducted by the Finnish Medicine Agency in 2015 (Kiiski et al. 2019) identified 43 medication review procedures. Almost half of them (n=22) were designed for older adults in primary care, mainly being established between 2013 and 2015. Fifteen practices were reported from government or municipality-funded hospitals; health care settings were not specified (Kiiski et al. 2019).

4.2.2 Patients and methods

This study was conducted at an ED ward, an acute, short-term care unit with 16 beds in a regional secondary care hospital (Satasairaala Central Hospital) in Finland. Patients from the emergency room are admitted to the ED ward for further medical observation up to one or two days, for specialist consultations, or before transfer to other wards in primary or secondary care, or for discharge.

This was a prospective study. Before the actual study, a 3-month pilot was conducted to establish and standardize the CMR procedure in ED. A paper form for CMR documentation and communication was developed during the pilot phase, piloted, and introduced to the ED physicians and nurses. The form was divided into two sections: 1) documentation of findings from ED pharmacist's review of medication for IP identification and recommendations for possible changes in the medication, and 2) documentation of ED physicians' final assessments and clinical decisions, for example confirming IPs identified by the pharmacist.

In the first phase of the study, all the adult patient admissions (≥18 years) to the ED short-term ward within the study period of 5 months were reviewed (Figure 5).



ED = emergency department; IP = Inappropriate prescribing.

Figure 5. Study flow (Study II).

4.2.3 Assessing the inappropriateness of pre-admission medications

Only prescribed pre-admission medications that the patient had been using before admission to ED were reviewed. The following definition for IP was adopted: "*prescribing medications that have more potential risk than potential benefit or prescribing that does not agree with accepted medical standards*" (Hanlon et al. 2001). This definition was used when the ED pharmacist judged whether the patient's medication was inappropriate. The following IP events were observed: 1) Significant drug-drug interactions (DDIs); 2) Incorrect doses considering patient's age or condition; 3) Incorrect frequency or duration of the treatment; 4) Medication with no indication; 5) Therapeutic duplication (prescribing and dispensing of two or more drugs from the same therapeutic category so that the combined daily dose puts the patient at increased risk of ADRs without additional therapeutic benefits) (Fulda et al. 2004), and 6) Untreated indication.

The ED pharmacist used electronic evidence-based medication risk management databases for identifying IP events. These databases were widely used in the Finnish social and health services system at the time of the study through the National Health Portal Terveysportti (The Finnish Medical Society Duodecim 2021a). Confirmed changes to medications were documented in medication records by the ED physicians. Any change in the medication based on CMR, including adding or discontinuing a drug, alternative dose, alternative route, time, or duration of use, was counted as an implemented change on medication charts.

4.2.4 Statistical analysis

For the descriptive analysis of the data, identified and confirmed IP events were inductively categorized (O'Connor et al. 2012). The first phase of the descriptive analysis included all the adult ED admissions with the CMR (Figure 5). The further descriptive analysis of IP events was targeted to older patients (≥65 years) because the majority of patients with at least one IP event were found to belong to this age segment. Quantitative variables were presented as means, standard deviations (SD), medians, and ranges (minimum and maximum). The Student's t-test was used to compare differences. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed using SPSS 26.0.

4.3 Are older people aware of potential risks related to benzodiazepines they are taking and has anything changed in risk awareness over ten years? (Study III)

4.3.1 Patients and methods

This was a descriptive study based on personal patient interviews. We compared two cross-sectional data sets collected from a primary care hospital's in-patients in one-month periods in 2004 and 2015. The same study protocols and practices were followed in both study periods. The study hospital was a mid-sized (191 beds) public primary care hospital in the City of Pori, Finland, with wards offering acute and rehabilitation specialist services in internal medicine, geriatrics, and neurology. The two acute wards with 28 beds each were selected for both study periods. Acutely ill patients were randomly directed to these wards.

4.3.2 Data collection

Patients aged ≥65 years admitted to both wards with an acute illness during the study periods, between 1 June and 30 June 2004, and 1 May and 30 May 2015 were included. Of all patients admitted to the wards, eligible patients using BZD for treatment of insomnia were interviewed after their cognitive function was assessed using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) on the first or second day after their hospitalization. Patients scoring ≥20 MMSE sum points were considered eligible to be interviewed. This cut-off point based on the MMSE was used to increase the reliability of patients' responses on the BZD use (Puustinen et al. 2007). Current regular and pro re nata (PRN; when required) medication use were reviewed by interviewing the patients during the first week after admission and from outpatient medical records. Only the baseline outpatient medical records were used; therefore, possible acute medication changes after admission to the ward were not considered. BZD use for three months or longer within a year (12 months) was defined as regular use.

In both study periods, each consented eligible patient using BZD was interviewed personally on their awareness of ten main potential risks related to the use of BZD. The selection of potential risks was based on statutory package leaflets (PLs) in harmonized use within European Union countries (European Commission 2009). During the personal face-to-face interviews, the researcher asked whether the patients were aware of the following ten potential risks related to BZD: 1) dependence, 2) interaction with alcohol, 3) withdrawal symptoms, 4) dizziness, 5) do not aid sleep in the long-term use, 6) reduced psychomotor performance and memory, 7) tolerance, 8) falls, 9) depression, and 10) muscle weakness. Patients' awareness of potential risks related to BZD use was scored by giving 1 point for each known adverse reaction, yielding a score range of 0–10.

Each eligible patient using BZD was also interviewed on their experiences of BZD withdrawal and their willingness to discontinue BZD therapy. Patients were asked whether they had withdrawal attempts, whether they had experienced BZD withdrawal symptoms, and whether they were willing to discontinue their BZD therapy at the time of the interview. There was no specific time frame set for these questions, for example for withdrawal attempts.

4.3.3 Statistical analysis

The $\chi 2$ test or Fisher's Exact test was used to test the differences in categorical variables. The significances of changes in all study patients and BZD users (with MMSE ≥20) were tested using the Wilcoxon signed-rank test. The differences of the mean sum scores, the mean ages and the mean number of medications, and the changes of mean sum scores between study periods were tested using the two-sample t-test, one-way analysis of variance, the Mann–Whitney U-test, or the Kruskal-Wallis test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS System for Windows, version 9.1 (SAS Institute Inc., Cary, NC, USA).

4.4 Research ethics (Study I, II, and III)

For study I, the local research ethics committee of Satasairaala Central Hospital (formerly Satakunta Central Hospital) was consulted. According to the research ethics guidelines in Finland, this kind of health services research, not including clinical interventions to patients, does not require a research ethics committee's opinion Regulations (Finnish Advisory Board on Research Integrity 2012). The pilot testing of the adapted and modified MSSA tool on the wards was conducted under the permission of the chief administrative physician. All data processing throughout the study was performed according to good scientific practice. The anonymity of the panelists and those involved in the pilot testing of the new tool was ensured. The ISMP was consulted, and permission to use the ISMP's MSSA tool for hospitals 2004 for this study was received.

Study II was conducted with the approval of the Institutional Review Board of Satasairaala Central Hospital and under the permission of the chief administrative physician. The study was carried out in accordance with the National Research Ethics Guidelines and Regulations (Finnish Advisory Board on Research Integrity 2012), which are in line with the Declaration of Helsinki (World Medical Association Declaration of Helsinki 2013). Written informed consent was obtained from participating patients. The Regional Ethics Committee, Turku Clinical Research Centre (Turku CRC), was also consulted. According to the Turku CRC's statement, additional approval from the Regional Ethics Committee was not required for this descriptive study. Turku CRC offers support and services for investigator-initiated clinical studies (Turku Clinical Research Center, CRC 2021). Its services are available to investigators at the University of Turku and in the Hospital District of Southwest Finland, including Satasairaala Central Hospital. At the time of this study, according to the National Research Ethics Guidelines and Regulations (Finnish Advisory Board on Research Integrity 2012), the Regional Research Ethics committee's approval was not required for clinical practice studies based on current care guidelines.

In Study III, both study periods were conducted with the approval of the Institutional Review Board of the Primary Care Hospital Services in the City of Pori, Finland. The study was carried out in accordance with the National Research Ethics Guidelines and Regulations (Finnish Advisory Board on Research Integrity 2012), which are in line with the Declaration of Helsinki (World Medical Association Declaration of Helsinki 2013). Written informed consent was obtained from participating patients. The Regional Ethics Committee, Turku CRC, was also consulted. According to the Turku CRC's statement, additional approval from the Regional Ethics Committee was not required for this observational study. At the time of this study, according to the research ethics guidelines in Finland (Finnish Advisory Board on Research Integrity 2012), Regional Research Ethics committee's approval was required only for research in which patients are exposed to a clinical intervention other than the routine clinical practice based on current care guidelines. Turku CRC stated that no such interventions were performed in this descriptive study.

5 RESULTS

5.1 Adapting and remodeling the US Institute for Safe Medication Practices' Medication Safety Self-Assessment Tool for Hospitals (Study I)

5.1.1 Panelists who participated in Delphi

A total of 26 experts were invited, of whom in total 14 participated. Participated panelists were health care experts from Finnish health care authorities, institutes, and organizations with pharmacy (n=4), medicine (n=2), and nursing (n=8) backgrounds. All of the 14 participated panelists completed every Delphi round.

5.1.2 Pre-Delphi modification of the Medication Safety Self-Assessment tool and Delphi rounds

The research team discarded a total of 117 items (51% of the original items) within the preliminary modification phase. Thus, the Delphi survey questionnaire for the first and second Delphi rounds included the remaining 114 items, of which 51 items needed clarification at the first panel. A total of 36 new items were suggested by the panelists. Needed clarifications were made, and all suggested 36 new items were included in the second round to be evaluated. After the first two Delphi rounds (consensus rate: 50%), a total of 13 original items and seven of the new items were discarded, and out of the accepted original items, a total of 32 were revised according to panelists' responses. Revisions consisted of splitting an item into two items, combining two items into one item, or minor changes due to organizational differences. A total of 130 items (101 original and 29 new items) were accepted to be evaluated in the third Delphi round. After the third Delphi round (consensus rate: 75%), five original items and five new items were discarded. The remaining total of 120 items (96 original items and 24 new items) were evaluated to obtain consensus (consensus rate: 75%) for the feasibility of the items at the fourth (final) Delphi panel. At the final round, five original items and only one new item were discarded. The finalized Delphi modified MSSA tool had 91 original items and 23 additional new items (Table 9). The obtained consensus at the third and fourth panel rounds varied between 75% and 100%; however, most items (103/114) obtained a consensus rate over 90%.

Table 9. Modification of the ISMP's MSSA tool for hospitals (items that reached consensus after four Delphi rounds).

Components of the original ISMPs MSSA tool for hospitals	Number of items in the ISMPs MSSA tool for hospitals	Number of suitable items for assessment after **preliminary modification**	Number of **applicable** items after 1st and 2nd Delphi panel rounds	Number of **desirable** items after 3rd Delphi panel round	Number of **feasible** items after 4th Delphi panel round (final)
1. Patient information	20	9	7	7	7
2. Drug information	30	9	9	8	7
3. Communication of drug orders and other information	15	6	6	6	6
4. Drug labeling, packaging and nomenclature	20	10	9	9	9
5. Drug standardization, storage and distribution	35	11	8	8	7
6. Medication device acquisition, use and monitoring	13	8	8	8	6
7. Environmental factors, workflow and staffing patterns	17	15	11	9	9
8. Staff competency and education	21	15	15	13	13
9. Patient education	11	11	10	10	10
10. Quality processes and risk management	49	20	18	18	17
Total ISMP	**231**	**114**	**101**	**96**	**91**
Additional items	**-**	***36***	***29***	***24***	***23***

ISMP = Institute for Safe Medication Practices; MSSA = Medication Safety Self-Assessment.

5.1.3 Remodeling the Delphi-modified medication safety self-assessment tool and pilot use

The Delphi-modified final MSSA tool was reorganized and regrouped under the six main components with sub-contents (Table 10) adapted from the recommendations by the MSAH to establish ward-based pharmacotherapy plans in Finnish hospitals (MSAH 2006).

Table 10. The remodeled Delphi-modified MSSA tool (items regrouped under six main components with sub-contents partly adapted from the Finnish Guidelines for Safe Pharmacotherapy 2006) (MSAH 2006).

I. Main working principles (17 original items + 6 additional items)
Description of medicines used and the medication management process in the unit
Ensuring and maintaining personnel's pharmacotherapeutic knowledge and skills
Clarifying personnel's responsibilities, obligations, and tasks in medication management
License practices (for example in administration of intravenous medications)
II. Pharmaceutical services (5 + 11)
Ordering, storing, and compounding medicines
On-site preparation
Return policy of medicines
Access to drug information
Guidance and advice
III. Medication use process (20 + 5)
Prescribing and transmitting the prescription
Labeling, distribution, and administration of medicines
Medication counseling and patient education
Evaluation of the effectiveness of pharmacotherapy
IV. Documentation and reconciliation (19 + 0)
Patient information
Drug information
Communication of drug orders and other information
V. Environmental factors, medication devices, and monitoring (20 + 1)
Working environment
Medication device acquisition, use, and monitoring
Systems for monitoring and follow-up of medications
VI. Clinical pharmacy services (10 + 0)
Medication review
Patient information
Drug information

MSSA = Medication Safety Self-Assessment; MSAH = Ministry of Social Affairs and Health (Finland).

The pilot units consisted of eight internal medicine wards that varied in specialty and size (diabetes, hematology, heart, nephrology, neurology, respiratory, and two surgery wards). The most fully or partly implemented items were found at component II, 'pharmaceutical services' (an average of 12 out of 16 items). The least implemented (poorly or not implemented) practices were found at component III, 'medication use process' (an average 8 out of 25 items). Improvements, i.e., identifying high-risk medications and implementing the double-checking practice,

safe storing, and labeling practices, were done in each subject ward based on the findings of the self-assessment results (Table 11).

Table 11. Major improvements made in the eight pilot wards using the modified and remodeled MSSA tool (Pilot test phase of Study I).

Components of the modified and remodeled MSSA tool	Major improvements made based on the use of the modified and remodeled MSSA tool
(I) Main working principles	Increased understanding and application of systems approach to MEs Improved openness in meetings on ME processing Improved staff education
(II) Pharmaceutical services	Safety-improved storage areas for various medications Updated protocols for preparation of IV medications
(III) Medication use process	Improved medication labeling Improved communication of medication orders Established double-check protocol Updated patient education protocols
(IV) Documentation and reconciliation	Updated protocols for safe medication in patients with renal and liver failure Updated protocols for safe use of opiates Improved identification of look-a-like medications Established policy on using patients' own home medication while in the hospital
(V) Environmental factors, medication devices, and monitoring	Improved safety check of infusion pumps Established safe storage instructions for electrolytes to be diluted before use (i.e., KCl) Improved awareness on estimating environmental factors from the risk management aspect
(VI) Clinical pharmacy services[1]	Entire component was defined as an area for development

MSSA = Medication Safety Self-Assessment; ME = Medication error; KCl = Potassium Chloride.

[1]: *At the time of Study I, there was no ward-based clinical pharmacy services available in the study hospital. Therefore, the component VI. Clinical pharmacy services were not included in the pilot tests, and the entire component VI was targeted as an area for development.*

According to the nurse managers of the eight pilot wards, adapted MSSA practice was found helpful in identifying and improving the high-risk practices in the medication management process. The majority (7 out of 8) of the nurse managers believed that the self-assessment could be made regularly, for example, every two years, to keep the pharmacotherapy plans updated. All nurse managers suggested the self-assessment practice being conducted and coordinated by the hospital pharmacy because hospital pharmacists have different perspectives than nurses and doctors working in the wards. Major points of criticism were related to time consumed during the self-assessments. All nurse managers of the pilot wards perceived that the self-assessment tool was too comprehensive and the practice was too time-consuming.

5.2 Collaborative medication reviews to identify inappropriate prescribing in pre-admission medications at emergency department short-term ward (Study II)

Altogether, pre-admission medications of 855 adult patients (64% women, 36% men) presented in the ED short-term ward were reviewed by the ED pharmacist during the 5-month study period. The pharmacist identified 83 (9.7%) of these patients with at least one IP event (mean 1.4 IP events per patient). The majority (81%, n=67) of the patients with IP events were older adults (≥65 years old). Therefore, further analysis on IP focused on this patient segment (Figure 5). The pharmacist identified a total of 94 IP events in 67 older adults (mean 1.4 IP events per patient). Of the 94 identified IP events, 58 (62%) were confirmed by the ED physicians, concerning 49 out of 67 patients (73%), leading to implemented changes in their medication records. The number of regularly used pre-admission medications in the older adults with identified IP events (n=67) ranged from 2 to 18 (median 7) (Table 12). The corresponding range for the older adults with confirmed IP cases (n=49) was 6 to 18 (median 9). Of them, 36 out of 49 (73%) were female, and 13 (27%) were male (Table 12). The mean age (p=0.03) and the mean number of pre-admission medication in regular use (p=0.01) were higher in confirmed IP events than in identified IP events (Table 12).

Table 12. Demographics for patients ≥65 years old with identified (n=67) and confirmed IP (n=49).

	Identified IP	**Confirmed IP**	**P-value**
Age, years Mean ± SD Median [Range]	76.4 ± 7.1 77 [65-93]	78.7 ± 6.2 80 [68-93]	0.03
Sex n (%)	Female 43 (64) Male 24 (36)	Female 36 (73) Male 13 (27)	NS
Number of pre-admission medicines in regular use Mean ± SD Median [Range]	8 ± 3 7 [2-18]	9 ± 2.5 9 [6-18]	0.01

IP = Inappropriate prescribing; SD = Standard deviation.

5.2.1 Types of inappropriate prescribing

The inductive categorization yielded the following three main types of IP events (O'Connor et al. 2012): 1) Misprescribing (prescribing medications that significantly increase the risk of ADEs); 2) Over-prescribing (prescribing medications for which no clear clinical indications exist); and 3) Underprescribing (omission of potentially beneficial medications that are clinically indicated for treatment or prevention of a disease) (Table 13).

Misprescribing was the most common type of IP identified (79% of the identified and 72% of the confirmed IP events), followed by over-prescribing (15% vs. 21%) and underprescribing (6% vs. 7%) (Table 13). Most of the misprescribing events were clinically significant DDIs (40% vs. 35%) and incorrect doses considering the patient's age or conditions (28% vs. 24%). Of the incorrect doses, those considering renal impairment (RI) were the most common ones (11% vs. 12%) (Table 13).

Table 13. Types of IP in the identified and confirmed IP events.

Types of IP	Identified IP (total= 94) n (%)	Confirmed IP (total= 58) n (%)	Implementation rate %
Misprescribing	**74 (79%)**	**42 (72%)**	**57**
Significant drug-drug interaction	38 (40%)	20 (35%)	53
Inappropriate medication or dose considering patient age or condition	26 (28%)	14 (24%)	54
incorrect dose in renal impairment	*10 (11%)*	*7 (12%)*	*70*
Incorrect frequency or duration of treatment	10 (11%)	8 (14%)	80
Over-prescribing	**14 (15%)**	**12 (21%)**	**86**
Medication with no indication	8 (9%)	6 (10,4%)	75
Therapeutic duplication	6 (6%)	6 (10,4%)	100
Underprescribing	**6 (6%)**	**4 (7%)**	**67**
Untreated indication	6 (6%)	4 (7%)	67

IP = Inappropriate prescribing.

5.2.2 The implementation rate of changes according to the type of inappropriate prescribing and the therapeutic group of the medicine

Identified IP events among the older adults led to a change in medications in 62% (implementation rate) of the cases. Implementation rate varied from 53% (significant drug-drug interactions) to 100% (therapeutic duplications). The highest (86%) implementation rate was in over-prescribing category, followed by underprescribing (67%). The lowest (57%) implementation rate was in misprescribing category (Table 13). Benzodiazepines (chlordiazepoxide, diazepam, oxazepam, and temazepam) and antidepressants (amitriptyline, citalopram, doxepin, and fluoxetine) were involved together in 33 out of 58 (57%) IP events (Table 14). Three drugs with strong anticholinergic effects (amitriptyline, doxepin, and oxybutynin) were involved in 19% of all cases (Table 14).

Table 14. Pre-admission medications involved in confirmed IP events (n=58).

Therapeutic Category/Drug	Therapeutic classes (ATC codes) of medications	Number of confirmed IP	Types of IP
Benzodiazepines		**17**	
Diazepam	N05BA01	6	M,O
Temazepam	N05CD07	5	M,O
Oxazepam	N05BA04	4	M
Chlordiazepoxide	N05BA02	2	M
Antidepressants		**16**	
Fluoxetine	N06AB03	5	M,O
Citalopram	N06AB04	5	M,O
Amitriptyline	N06AA09	3	M,O
Doxepin	N06AA12	3	M
Anticholinergics		**5**	
Oxybutynin	G04BD04	5	M
Antithrombotic agents		**4**	
Warfarin	B01AA03	2	M,U
Aspirin (as an antiplatelet agent)	B01AC06	2	U
Opioid analgesics		**4**	
Tramadol	N02AX02	4	M
Antidiabetics		**3**	
Metformin	A10BA02	3	M,U
NSAIDs		**3**	
Ibuprofen	M02AA13	3	M
Antipsychotics		**2**	
Chlorpromazine	N05AA01	2	O
Agents for obstructive airway diseases		**2**	
Theophylline	R03DA04	2	M
Diuretics		**1**	
Triamterene	C03DB02	1	M
Antiepileptics		**1**	
Carbamazepine	N03AF01	1	M
Total		**58**	

IP = Inappropriate prescribing; NSAID = Non-steroidal anti-inflammatory drugs; M = Misprescribing; O = Over-prescribing; U = Underprescribing.

5.3 Are older people aware of potential risks related to benzodiazepines they are taking, and has anything changed in risk awareness over ten years? (Study III)

5.3.1 Characteristics of the study patients

The study sample in 2004 consisted of 188 patients, of which 164 were aged ≥65 years. BZD users who scored eligible in MMSE were interviewed (n=37). In 2015, 166 patients were admitted, of which 105 were aged ≥65 years. BZD users who scored eligible in MMSE (n=31) were interviewed (Table 15).

Table 15. Characteristics of the study patients (BZD users: n=37 in 2004 and n=31 in 2015).

		All study patients			BZD users		
		2004 (n = 164)	**2015** (n = 105)	p	**2004** (n = 37)	**2015** (n = 31)	p
Gender n (%)	Female	128 (78)	64 (61)	-	30 (81)	25 (81)	-
	Male	36 (22)	41 (39)	-	7 (19)	6 (19)	-
Age (y) Mean ± SD		81.6 ± 6.8	81.9 ± 8.1	0.767	80.3 ± 5.4	80.2 ± 8.6	0.951
Total number of medicines in use, Median [LQ, UQ]	All	8 [6,12]	12 [9,16]	<.0001	10 [7,15]	16 [12,18]	<.001
	Regular use	7 [5,11]	9 [6,11]	0.007	8 [6,12]	11 [7,12]	0.664
	PRN use	1 [0,2]	3 [1,6]	<.0001	1 [0,3]	6 [4,6]	<.001
Use of at least one BZD, n (%)	All	76 (46)	36 (34)	0.05	NE	NE	NE
	Regular use	51 (31)	13 (12)	<.005	21 (57)	10 (32)	<.005
	PRN use	36 (22)	27 (26)	0.477	17 (40)	25 (81)	<.005
Concomitant use of BZD (two or three), n (%)	Regular or PRN use	20 (12)	7 (7)	0.110	11 (30)	6 (19)	0.132

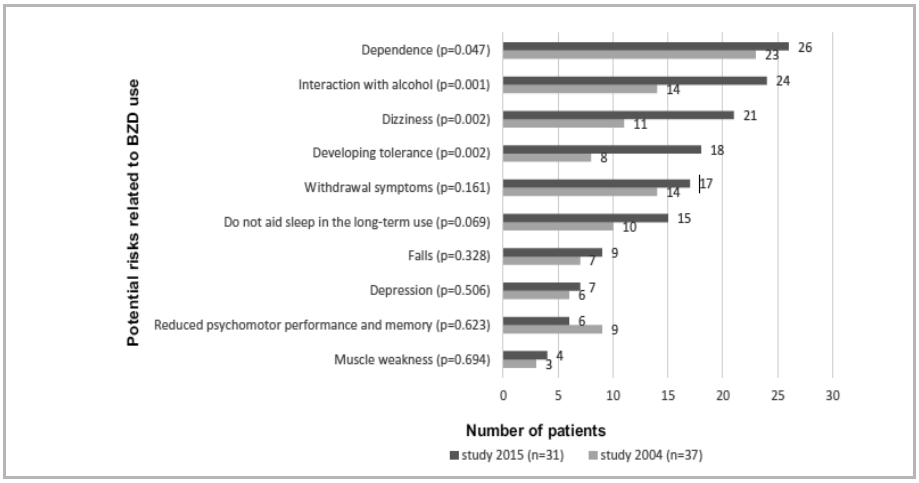
BZD = benzodiazepines and related drugs; PRN use = pro re nata (when required);
SD = standard deviation; LQ = lower quartile; UQ = upper quartile; NE = not estimable.

The mean age of the BZD users did not differ between the study periods in 2004 and 2015 (80.3 ± 5.4 vs. 80.2 ± 8.6, respectively). The female gender was more common in both study periods among BZD users (81% in 2004 and 2015). The total number of medications in use had increased significantly among BZD users (p<0.001), also PRN use had increased (p<0.001). The regular use of at least one BZD among BZD users had declined (p<0.043), while PRN use had increased (p<0.003). The difference in concomitant use of BZD between the two study periods was not significant (Table 15).

5.3.2 Patients' awareness of potential risks related to benzodiazepine use

The patients' awareness of potential risks related to BZD had increased between the study periods on dependence, interaction with alcohol, dizziness, and developing tolerance (Figure 6).

In 2004, dependence was the only potential risk that more than half of the patients (62%) were aware of, while in 2015, more than half of the patients were aware of dependence (84%), interaction with alcohol (77%), dizziness (68%), developing tolerance (58%) and withdrawal symptoms (55%). The awareness of other potential risks remained unchanged, muscle weakness being the least known potential risk in both study periods (8% vs. 13% of the patients being aware of it as a potential risk, respectively) (Figure 6).

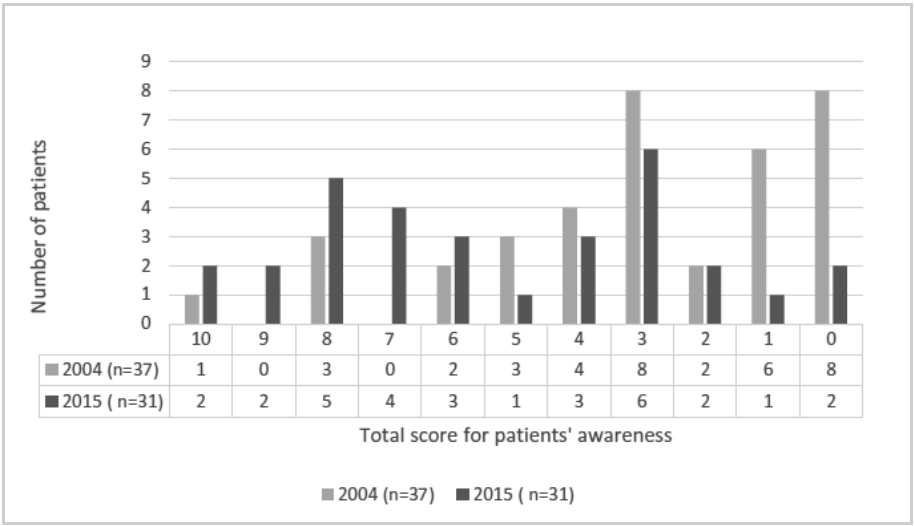


BZD = benzodiazepines and related drugs.

Figure 6. Patients' awareness of potential risks related to the use of BZD in 2004 and 2015.

The mean risk awareness score in 2004 and 2015 was 3.0 ± 2.6 vs. 5.3 ± 2.9, respectively (p=0.001). In 2004, six out of 37 patients (16%), while in 2015, 16 out of

31 (52%) had higher than 6/10 risk awareness scores. The number of patients who were not aware of any of the ten potential risks (total score=0) was eight (22%) in 2004, while two patients (7%) were found with zero total scores in 2015 (Figure 7).



BZD = benzodiazepines and related drugs.

Figure 7. Total scores (0–10 points) for patients' awareness of potential risks related to BZD use.

No significant differences were found between study periods in patients with BZD withdrawal attempts, the patients who experienced BZD withdrawal symptoms, or patients willing to discontinue BZD therapy (Table 16).

Table 16. BZD withdrawal and desire for discontinuing BZD therapy in BZD users (BZD users: n=37 in 2004 and n=31 in 2015).

BZD withdrawal and desire for discontinuing BZD therapy in BZD users	**2004** (n=37)	**2015** (n=31)	*p*
Patients with BZD withdrawal attempts n (%)	12 (32)	7 (23)	*0.367*
Patients experienced BZD withdrawal symptoms n (%)	9 (69)	2 (33)	*0.319*
Patients with desire for discontinuing BZD therapy n (%)	12 (35)	8 (26)	*0.408*

BZD = benzodiazepines and related drugs.

6 DISCUSSION

6.1 Adapting and remodeling the US Institute for Safe Medication Practices' Medication Safety Self-Assessment Tool for Hospitals (Study I)

It was possible to adapt the original US ISMP's MSSA tool for another health care system despite differences in legislation and hospital settings by using the Delphi consensus method. The Delphi-modified and remodeled Finnish MSSA tool was valid for assessing medication management practices in central hospital wards with different medical specialties. Prior to the Delphi rounds, nearly half of the items of the original MSSA tool were discarded due to Finnish legislation and medication management practices on the hospital wards. On the other hand, a significant number (n=23) of new items were derived from the Finnish health care context and practices and included in the final tool. It means that 20% of the items in the modified tool were derived from the Finnish health care context and practices. This demonstrates that the adaptation process needs to consider contextual aspects: it cannot be based solely on linguistic translation. Some of the final modified version items were kept even though the practices did not exist at that stage in Finland. The items were regarded to perform as a stimulus for their desired adaptation.

To our knowledge, this study is the only reported study to adapt and remodel the original ISMP MSSA tool for hospitals for another health care system in another country. Three previously published studies report results from using the original ISMP MSSA tool (versions 2000 and 2011) for hospitals in the USA (Lesar et al. 2003, Smetzer et al. 2003, Vaida et al. 2014). The cross-sectional survey of U.S. hospitals (n=1435) using the ISMP's MSSA tool in 2000 revealed that the participating hospitals scored highest in areas related to drug storage and distribution, environmental factors, and medication labeling, while the lowest scores were reported in areas related to patient information, communication of medication orders, patient education and quality processes, such as double-check systems and organizational culture (Smetzer et al. 2003). Later in 2011, another survey of U.S. hospitals (n=1310) using the 2011 updated ISMP's MSSA tool showed that the largest percent improvements were in core characteristics related to communication of drug orders, patient education, and quality processes and risk management. Hospitals with a medication safety officer scored higher in all key elements than hospitals without (Vaida et al. 2014). This pilot study in Finland in 2010 consisted of eight central hospital wards within the same hospital and identified well-implemented practices in *drug storage and distribution*. At the same time, items related to *medication order communication and patient education* were most poorly implemented.

Despite being time-consuming, the pilot users were convinced that all the items of the adapted tool were necessary to assess the safety of medication practices in the pilot wards. Pilot users suggested that MSSAs should be carried out on a regular

basis, for example, every two years, to keep the unit-based pharmacotherapy plans updated. Pilot users also suggested that the self-assessments should be managed and coordinated by the hospital pharmacy as was done in the pilot project.

After this pilot study was conducted in 2010, pharmacist-conducted MSSAs have performed as a facilitator for enhanced and goal-oriented collaboration between hospital pharmacies and clinical wards in improving the safety of medication practices. One of the six main components of the Finnish MSSA tool was clinical pharmacy services. At the time of the pilot study, no clinical pharmacy services were available in the Satakunta Hospital District. Therefore, clinical pharmacy services were selected as an area for strategic development in the District. Since then, during the last ten years, clinical pharmacy services have been established in many clinical wards of the Satasairaala Central Hospital (formerly Satakunta Central Hospital), including each pilot ward in the study. The positive experiences obtained from conducting the self-assessment in the pilot study quite likely have contributed to this development. The same trend can be seen nationally in Finland in implementing and extending range of clinical pharmacy services in hospitals (Schepel 2018, Schepel et al. 2019).

At the national level, the MSSA tool's contents may have helped shape the contents of the Guidelines for Safe Pharmacotherapy by the Ministry of Social Affairs and Health. The first version of the guidelines (2006) included a list of safety areas in medication (MSAH 2006), but it did not have much explicit content under those safety areas. The health care units were recommended to establish a pharmacotherapy plan based on the guidelines. However, it was unclear what types of safety practices they were expected to implement. The Finnish MSSA tool for hospitals was able to provide the suggested contents under these safety areas, i.e., how to report and analyze a medication error for learning purposes, minimize risks related to various steps in the medication process, and manage high-risk medicines, etc.

The MSSA tool has created awareness of the crucial issues of medication risk management. One such key area in the MSSA tool is risk management practices for high-risk medications. The first version (2006) of the Guidelines for Safe Pharmacotherapy had no mention of high-risk medicines, but they were included in the following version of the Guidelines in 2015. The care units were recommended to identify high-risk medications used in their routine practice and prepare in-house operating instructions for managing these risks. The current version of the Guidelines, published in 2021, suggests units identify and learn from the risks related to these medications and prepare for managing these risks by establishing systemic defenses.

Soon after this study was conducted, the pharmacist-conducted practice using the Finnish MSSA tool for hospitals was called medication safety audit, which evolved to a multi-step risk management process. In addition to the basic self-assessment step, medication safety audits started to include other steps in the clinical ward, such as an introductory meeting before the self-assessment, observation of the medication practices, and a meeting to discuss the audit report results, prioritize practices

needing improvement and establishing an action plan for implementing the changes. In this way, medication safety audits have helped establish and enhance cooperation between clinical wards and the hospital pharmacy. They have helped make the cooperation more concrete and focused on medication safety issues important in each health care unit. Furthermore, audits have helped to strengthen leadership in medication management and define tasks and responsibilities of each professional involved in it.

The MSSA tool and medication safety audits may have played a stimulating role in many other medication safety initiatives adopted in Finland during the last ten years. Among the most important initiatives have been establishing regional medication safety officers that work with regional patient safety officers in health care districts. The first position for a medication safety officer in Finland was established in the Helsinki University Hospital (Hospital District of Helsinki and Uusimaa), Finland's largest hospital district, in 2016 (Schepel 2018). A few years later, another position for a medication safety officer was established in Tampere University Hospital (Hospital District of Pirkanmaa), with medication safety audits being suggested as one of the key tasks of this new officer (Kankaanpää et al. 2020).

The Finnish MSSA tool for hospitals was updated in 2021 (Oksa et al. 2021). The previously adopted Finnish MSSA tool (2008) and the ISMP MSSA tool 2011 (270 items) were evaluated simultaneously by the Delphi consensus method, including two Delphi rounds. The updated MSSA tool contained significantly more items (229 items) than the previous version (114 items) (Celikkayalar 2016). The updated Finnish MSSA tool for hospitals consists of eleven thematic sections reflecting the current safe medication practices in Finnish hospitals: 1. Patient information (10 items), 2. Drug information (19), 3. Communication of drug orders and other drug information (21), 4. Drug labeling, packaging, and nomenclature (10), 5. Drug standardization, storage, and distribution (26), 6. Medication device acquisition, use, and monitoring (18), 7. Environmental factors, workflow and staffing patterns (16), 8. Staff competency and education (23), 9. Patient education (14), 10. Quality processes and risk management (48) and 11. Organizational level items (24). Compared to the previously adopted version (Celikkayalar et al. 2016), the new updated Finnish MSSA tool includes organizational level criteria adopted from the original ISMP MSSA tool (ISMP 2011; Oksa et al. 2021). Therefore, the updated MSSA tool may help to improve the organizational level policies and practices in medication risk management (for example electronic patient record systems). In addition, the new updated Finnish MSSA tool includes many unique items grouped under the section: Quality processes and risk management (Section 10). The previously adopted version (Celikkayalar et al. 2016) was based on the ISMP's MSSA tool for hospitals 2004 (231 items), while an extended version, ISMP's MSSA tool for hospitals 2011 (270 items), was used for the new updated Finnish MSSA tool for hospitals (ISMP 2011; Oksa et al. 2021).

Strengths and limitations of the study

As previously discussed, this study achieved an essential goal by developing and piloting the first MSSA tool for Finnish hospitals. The Finnish MSSA tool developed by this study was found helpful in routine practice in the health care units. It also

may have had a substantial influence on creating safe medication practices at the national level in Finland. The success of the developed MSSA tool shows that the Delphi consensus method used in this study was a suitable approach for this type of future research. The Delphi method used in this study had many advantages, i.e., gathering information from a wide range of topics based on the consensus of health care experts, a four-round process (applicability, desirability, and feasibility of the MSSA tool items were evaluated) to make further discussion possible for the panelists. The Delphi method also ensured the anonymity of the panelists. Despite the many advantages, the Delphi method does not provide definitive results because the results are based on opinions. It is possible that some of the panelists participated more actively than others. It is also possible that panelists even interpreted the items in different ways. As a limitation of the pilot phase, it must be kept in mind that the pilot users' perceptions are summarized from eight inpatient wards in one teaching, middle-sized secondary care hospital in Finland. This number of wards was considered sufficient for pilot testing the modified MSSA tool. Although the Finnish MSSA tool was used successfully in many various hospitals after this study, a pilot phase including several health care units from different settings could have improved the strength of this study.

6.2 Collaborative medication reviews to identify inappropriate prescribing in pre-admission medications at emergency department short-term ward (Study II)

The CMR practice was able to identify IP in pre-admission medications of about one-tenth of ED patients. The following observations were made of the incidence and type of IP events: 1) IP in pre-admission medication was most common in older adults; 2) majority of the IP events were related to misprescribing because of clinically significant DDIs, incorrect doses, frequency, or duration of treatments; 3) benzodiazepines and antidepressants were the medicines most commonly involved in IP events, followed by other medicines widely used in older adults, but considered as high-alert medicines or PIMs to be used with caution in this age segment of adults, for example anticholinergics.

This study found that most (81%) of the patients admitted to the ED short-term ward with at least one IP event in their pre-admission medications were patients aged 65 years or older. This indicates that CMR in the ED units could be focused on this patient segment in the circumstances of scarce resources. IP events identified in this research are in line with the risks identified in the previous studies (Thomas and Thomas 2019). In this study, such commonly used PIMs as benzodiazepines and antidepressants appeared in more than half of the IP events confirmed by the ED physicians. The BZD alone (diazepam, temazepam, oxazepam, chlordiazepoxide) were related to almost one-third (30%) of the confirmed IP events with implemented changes. Even though a previous national register-based study observed a declining trend in BZD use in Finland from 2006 to 2014, the long-term use remained high, particularly in older adults (Kurko et al. 2018). Another earlier national register study based on reimbursement data found that more than one-third of the total PIM use was associated with BZD in older adults in Finland in 2007 (Leikola et al. 2011). In that study, temazepam was the most commonly reimbursed PIM. Previous studies have suggested actions to reduce IP concerning benzodiazepine use in older adults. These actions include training physicians and other health care providers in geriatric pharmacotherapy and psychotropic deprescribing (Leikola et al. 2011, Kurko et al. 2018) providing computerized decision-making support and alerting systems for physicians (Leikola et al. 2011) involving pharmacists in medication reviews (Leikola et al. 2011), as well as enhancing patient involvement and improving their awareness of potential risks related to BZD they are taking (Leikola et al. 2011, Kurko et al. 2018). For long-term BZD users, benzodiazepine withdrawal interventions have been suggested (Salonoja et al. 2010, Leikola et al. 2011, Lähteenmäki et al. 2014, Kurko et al. 2018).

The present study indicates that well-coordinated CMR practice in the ED setting could effectively identify IP in benzodiazepine use and use of other PIMs in older adults. We also found that older study participants identified with IP events commonly used drugs with strong anticholinergic effects (amitriptyline, doxepin, or oxybutynin). These medicines were involved in one-fifth of the implemented IP events. These highly anticholinergic sedating drugs cause, for example orthostatic hypotension, leading to falls (The National Current Care Guidelines 2021, Finnish

Medicines Agency FIMEA 2021). Therefore, they are recommended to be avoided according to the national IP evaluation criteria used in this study. The same recommendation is given in the latest Beers criteria, internationally among the most commonly used explicit criteria for identifying PIMs in older adults (American Geriatrics Society 2019). Although the widely recognized Beers (American Geriatrics Society 2019) or STOPP/ START (Ryan et al. 2009) criteria was not directly used in this study, their information contents were incorporated in the electronic medication risk management tools was used within the electronic evidence-based medication risk management databases for identifying IP events (Study II: Table 1). These databases were widely used in the Finnish social and health services system at the time of the study through the National Health Portal, "Terveysportti" (Study II: Table 1). The national databases are regularly updated according to the most recent scientific evidence, also covering such PIM criteria as the Beers (American Geriatrics Society 2019), STOPP/START criteria (Ryan et al. 2009) and Laroche list (Laroche et al. 2007).

A majority (79%) of the IP events in pre-admission medications of older ED ward patients were related to misprescribing, mainly contributing to clinically significant DDIs (40% of the misprescribing cases). The high rate of DDIs can be partly explained by polypharmacy, common in older adults, making them a high-risk population for DDIs (Sánchez-Fidalgo S et al. 2017). Studies have shown that physicians are aware only of a minority of actual clinically significant DDIs (Toivo et al. 2016). Although most of the identified IP events in the present study were clinically significant DDIs, the implementation rate of changes was the lowest (53%) compared to other IP subcategories. This result means clinically significant DDIs were common, but physicians confirmed the identified DDIs only in about half of the cases. This may be because patients did not present symptoms that could have been regarded as DDI-induced in many identified IP events. Therefore, physicians did not want to change the medication without signs of DDI-induced harmful effects. However, in these DDI cases with the uncertainty of their effects, physicians, after negotiating with the ED- pharmacist, added a note to the identified patient record but did not confirm the DDI for a possible later notice.

According to this study, 10% of the IP events in the older patients admitted to the ED ward were dosage adjustment requirements due to renal impairment (RI). Incorrect dosing considering RI was presented in nearly half of the identified and implemented misprescribing events. RI-related inappropriate medication has been identified as a significant problem also in other studies in acute care; it has been reported that a concerning amount of prescriptions requiring dosage adjustments according to renal function remain unadjusted (van Dijk et al. 2006, Aronof and Aronof 2014; Desmedt et al. 2018). A previous study found that nearly 40% of the patients had impaired renal function at hospital discharge (van Dijk et al. 2006). Approximately 25% of the prescribed drugs for these patients required dosage adjustment. However, only 60% of the prescriptions were adjusted according to the recommendations (van Dijk et al. 2006). Another study suggested a collaboration model with clinical pharmacists to improve compliance with the clinical decision support system recommendations (Desmedt et al. 2018).

Strengths and limitations of the study

The main strength of our study was to use advanced, electronically available up-to-date guidelines (National Health Portal, "Terveysportti") integrated into the patient administration system (Study II, Table 1). Finland has a long history of national evidence-based clinical guidelines that are widely and routinely used throughout the social and health services system (Toivo et al. 2018); therefore, they were reliable tools to identify IP among patients in this study. These Guidelines are widely available in electronic format via the national health portal Terveysportti (The Finnish Medical Society Duodecim 2021a), making their use feasible at the point of care. They include up-to-date care and treatment recommendations, pharmaceutical information, and numerous medication risk management applications designed to help everyday activities (Study II: Table 1). The Guidelines are based on the best available scientific and clinical evidence and are continuously updated (The Finnish Medical Society Duodecim 2021b). The "clinical eye" of professionals is always needed to interpret information from the databases to make therapeutic decisions and communicate them to patients and the care team involved.

CMR practice was proved to be a feasible method for enhancing prospective medication risk management of patients admitted to ED short-term ward. However, this study has some limitations to consider when interpreting results. The study was relatively small and included only one regional ED in the Satakunta health care district. It is also difficult to compare studies reporting the impact of medication review interventions on IP because of the large variety, for example in the interventions, patient care settings with differing levels of communication culture in organizations, and a variety of criteria and methods used to assess inappropriateness in medications (Thomas and Thomas 2019). This study also did not include a follow-up phase after the discharge of the patients with the confirmed IP to see the impact of the implemented changes on their health and quality of life. This study focused on reviewing pre-admission medications of ED patients (prescribed medications). Thus, we did not summarize any therapies prescribed during medication changes, including non-pharmacological treatments. Neither did we focus on possible alternative non-pharmacological therapy recommendations by the ED pharmacist. This would be an interesting potential topic for further research to understand patient care decisions at ED wards better.

Practical implications

This study had the power to push forward the CMR model in the ED short-term ward in the Satasairaala Hospital in Pori. The collaborative model of the pharmacist, physician, and nurse has become a systematic part of routine practice. A geriatric nurse has also been integrated into the practice, making selecting patients for the CMR easier. An additional clinical pharmacist was also hired to ensure resources for the quality of the CMR practice. Currently, the CMR practice is being adapted to some other units of the health care district; the Unit of Neurology within the same Hospital and a primary care unit within the Satakunta Hospital District. CMR practices have become more common in various care settings in Finland since our study was conducted (Schepel et al. 2019; Kiiski et al. 2019; Toivo et al. 2019; Auvinen et al. 2021).

6.3 Are older people aware of potential risks related to benzodiazepines they are taking and has anything changed in risk awareness over ten years? (Study III)

This study investigated the change in older patients' awareness of the potential risks related to their BZD medications in 2004 and 2015. To our knowledge, this study is the first study to investigate directly the patients' awareness of potential risks related to their BZD use based on personal interviews. We found that older patients' awareness of potential risks related to their BZD use had increased; however, most patients were not aware of such potential risks as reduced psychomotor performance and memory, falls, depression, and muscle weakness. Awareness of the potential risk of dependence, interaction with alcohol, dizziness, and developing tolerance had improved. We also found that overall BZD use had declined, but PRN BZD use had increased. Despite improved patient awareness, no significant change was found in the willingness to discontinue BZD therapy. Previous research in the Satakunta health care district that aimed on improving the safety of medication use in the aged (Salonoja et al. 2010, Puustinen et al. 2011, Salonoja et al. 2012, Puustinen et al. 2012, Lähteenmäki et al. 2014, Puustinen et al. 2014, Puustinen et al. 2018, Lähteenmäki et al. 2019) may have contributed to the positive results of this study: the overall improvement in patients' awareness of the potential risks related to their BZD use and the decline in overall BZD use.

This study had the opportunity to compare findings in the same health care organization between approximately ten years to determine what has changed in the older patients' awareness of potential risks of BZD use. The same study protocol and practices were followed in both study periods to facilitate the comparability of the results. This study covered quite the same period as a national register-based study that observed a declining trend in BZD use from 2006 to 2014 (Kurko et al. 2018). Despite the observed decline, the long-term use remained high, particularly in older adults. This overall high long-term BZD use may be due to the common use of BZD drugs such as clonazepam and zolpidem: their use and long-term use had even increased in older adults (Kurko et al. 2018). Another national register study found that more than one-third of the total PIM use was associated with BZD in older adults in 2007 (Leikola et al. 2011). In that study, temazepam was the most commonly reimbursed PIM. The authors of both above-mentioned national studies (Kurko et al. 2018, Leikola et al. 2011) suggested several actions be taken to influence the use and long-term use of BZD in older adults. These actions included training physicians and other health care providers in geriatric pharmacotherapy and psychotropic withdrawal, providing computerized decision-making support and alerting systems for physicians, and involving pharmacists in medication reviews (Leikola et al. 2011). Researchers also suggested regularly monitoring national trends in PIM use (Leikola et al. 2011), especially the duration of BZD use (Kurko et al. 2018). Some of the recommended actions highlighted the need to enhance patient involvement. The researchers noted that a considerable proportion of repeat prescriptions of BZD were prescribed without a face-to-face consultation (Kurko et al. 2018). They suggested that the first prescription and the first repeat prescription of a BZD should be carefully considered (Kurko et al. 2018). For the long-term BZD users, BZD withdrawal interventions were suggested (Leikola et al. 2011; Kurko et al.

2018), considering BZD withdrawal requires strong commitment and motivation from both the patient and the health care professionals (Salonoja et al. 2010; Leikola et al. 2011; Salonoja et al. 2012; Lähteenmäki et al. 2014; Kurko et al. 2018)

Given how common BZD use and long-term use are in older adults, surprisingly little user-centered research was found, for example concerning awareness of potential risks or communicating about the risks with BZD users (Tannenbaum et al. 2014, Sirdifield et al. 2017, Webster et al. 2017, Sake et al. 2019). As the evidence on the BZD risks has been growing, it reflects to leading international and national PIM criteria (American Geriatrics Society 2019, Finnish Medicines Agency Fimea 2021). An interesting question is why this risk information is not shared with older BZD users to a greater extent than this study found? It would be interesting to investigate further whether better risk awareness of BZD users may affect their willingness to discontinue long-term BZD use. Our small-scale study did not show this association. However, in our previous intervention study carried out in the same hospital as the present study, one-time counseling by a geriatrician on BZD use, including counseling on potential risks of these medicines, helped significantly to reduce the BZD use, these effects persisting for the total 12-month intervention period (Salonoja et al. 2010). More such intervention studies with BZD user-centered withdrawal practices are needed. On the other hand, more awareness should be created of non-pharmacological treatments for insomnia, which are currently emphasized as the primary forms of treatment in care guidelines (American Geriatrics Society 2019; The Finnish Medical Society, Duodecim 2020). Also, awareness of prolonged-release melatonin as an option to reduce BZD use in the treatment of insomnia should be promoted (Clay et al. 2013, Lähteenmäki et al. 2014). Melatonin, a non-sedative hypnotic, has been demonstrated clinically relevant efficacy on sleep quality with a good safety profile, without risks such as dependence and withdrawal effects (Wade et al. 2007, Wade et al. 2010; Clay et al. 2013).

This study indicates that patients were not aware of some of the important potential risks of their BZD, such as reduced psychomotor performance and memory, falls, depression, and muscle weakness. These findings suggest that patient education and communication practices should be enhanced to improve patients' awareness of the potential risks of BZD they take. Health-care professionals, including pharmacists, need to recognize patients' risk perceptions better and use effective communication strategies to ensure better patient involvement when BZD use is considered the best therapeutic choice for their condition.

Strengths and limitations of the study

The primary focus of this study was to explore patients' risk awareness related to their BZD use. We developed a scoring system to evaluate the risk awareness over time, based on personal interviews. We were able to generate comparable findings between two study periods with a time difference of 11 years. The main limitation of this study is the relatively small number of study participants derived from the local health care organization. Further studies are needed with a larger number of patients. Future studies should also focus on older patients' willingness to discontinue BZD therapy and how it is influenced by their awareness of the potential risks these medicines pose them.

6.4 Practical implications for future research and practice

Studies of this thesis were conducted at a regional health care district level. In the Satakunta health care district, there have been numerous epidemiological research on improving the safety of medication use in the aged (i.e., prevention of medication-related falls and decline in cognition) coordinated by Professor Sirkka-Liisa Kivelä and her research teams in the 2000s (Jaatinen et al. 2007, Puustinen et al. 2007, Sjösten et al. 2008, Salonoja et al. 2010, Puustinen et al. 2011, Salonoja et al. 2012, Puustinen et al. 2012, Lähteenmäki et al. 2014, Puustinen et al. 2014, Nurminen et al. 2014, Puustinen et al. 2018, Lähteenmäki et al. 2019). Researchers have been supported within the Satakunta health care district throughout the years by in-house doctoral program training courses. These in-house courses have been beneficial also for this thesis, especially at the early stages of the work. Supported research studies have helped develop new practices and activities. The research studies of this thesis are good examples that have led to the development of medication safety audits and clinical pharmacy activities within the health care district.

In 2023, the health and social services reform will restructure the organization of public health care and social welfare services in Finland. The regional health care districts will be transformed into the *wellbeing services counties*. The main goal of the reform is to ensure equal, quality, and safe health and social services for all (MSAH 2021c). There is also a particular aim to make pharmaceutical services more cost-effective and to improve medication safety. Pharmaceutical services will be reformed on a long-term basis, taking into account the roadmap presented by the Ministry of Social Affairs and Health in 2019 (MSAH 2021d). There are substantial opportunities and roles for the hospital pharmacies to promote the rational use of medicines and manage pharmacotherapy costs within the regional health care district (in the future, the wellbeing services counties). This thesis has identified the following needs to improve medication safety in the future:

1. A national level of coordination is needed to maintain the different versions of the updated MSSA tool for various health care units and practices such as hospitals (Oksa et al. 2021), community pharmacies (Teinilä et al. 2012, Hämäläinen et al. 2019), managing high-risk medications (Schepel 2018) and preparation of parenteral medicines for use (Suvikas-Peltonen et al. 2017). As the original US ISMP MSSA tool for hospitals is developed based on the data analyzed from the ME reports from the US hospitals, the Finnish reporting system for MEs could be used to update the Finnish MSSA tool in the future (Study I).

2. A national level of coordination is also needed to describe better and standardize hospital clinical pharmacy services to get them better integrated into routine care. Other health care professionals should also be involved in developing these services. Health care providers should be well-informed about these collaborative practices and their benefits. As part of this, health care organizations should more explicitly define and describe clinical pharmacists' tasks and responsibilities in routine practice (Study I and II).

3. Future research should focus on assessing the impact of the CMR practice in the ED short-term ward to explore whether CMR practice in the ED could prevent re-admissions. Another interesting topic would be to explore the root causes of the IP identified by the clinical pharmacist in the home medications of the ED patients (Study II). In the future, the ED CMR model can be adapted to other types of health care units within the Satakunta Hospital District (including also the primary care units). Future research should explore the possibilities of these adaptations, especially from the perspective of the upcoming health care reform in 2023 (Study II). In the future, clinical pharmacy services in hospitals should be improved from the patient-oriented approach. Current clinical pharmacy services have many logistical elements that limit the clinical pharmacists' actual contributions to patient care-oriented work (Study II).

4. The CMR practice should also focus on the risk awareness of the patients. It is not enough only to identify and make the needed changes in medication. It is also essential to ensure that patients are aware of their medications and the risks related to their medications. Future research should investigate risk awareness of other high-risk medications, such as other central nervous system drugs, especially in older users. Risk awareness studies should also focus on developing patient-oriented interventions and follow-ups to identify the best effective and cost-effective practices to enhance patient involvement in medication risk management by improving their risk awareness (Study II and III).

7 CONCLUSION

The following conclusions can be drawn based on the findings of Studies I-III:

- It was possible to adapt the US ISMP's Medication Safety Self-Assessment (MSSA) tool for hospitals in Finland for another hospital setting. The modified MSSA tool can be used for a hospital pharmacy coordinated audit to identify safety risks in medication use in health care units in hospitals in Finland. The modified MSSA tool supports long-term medication safety initiatives, particularly establishing ward-based pharmacotherapy plans guided by the Finnish Ministry of Social Affairs and Health (MSAH). Despite being time-consuming, the pilot users were convinced that all the items of the adapted tool were necessary to assess the safety of medication practices in the pilot wards (Study I).
- The pharmacist-led collaborative medication review (CMR) practice identified inappropriate prescribing (IP) in pre-admission medications of nearly one-tenth of ED patients. Most of the IP events were related to misprescribing because of clinically significant DDIs, incorrect doses, frequency, or duration of treatments. Older patients using BZD and drugs with strong anticholinergic effects should be paid special attention to ED admissions (Study II).
- Older BZD users' awareness of potential risks related to BZD use (dependence, interaction with alcohol, dizziness, and developing tolerance) was improved between 2004 and 2015. However, most patients were unaware of such potential risks as reduced psychomotor performance and memory, falls, depression, and muscle weakness. BZD use had declined, but PRN BZD use increased. Despite the improvement in patients' awareness, there was no significant change in their willingness to discontinue BZD therapy. Enhanced patient education and communication approaches with appropriate assessment methods for risk awareness are needed (Study III).

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