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AUTOMATED DOSE DISPENSING SERVICE FOR PRIMARY CARE PATIENTS AND ITS IMPACT ON MEDICATION USE, QUALITY AND SAFETY

Juha Sinnemäki

DOCTORAL DISSERTATION

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ABSTRACT

Polypharmacy, i.e. concomitant use of several drugs is common among older adults. This increases the risk of using drugs that are potentially inappropriate and harmful for geriatric patients. Automated dose dispensing (ADD) is a procedure that has been implemented in some European countries, particularly in the Nordic countries and the Netherlands to manage these risks in primary care. In the ADD service, regularly used medicines are machine-packed into unit-dose pouches according to administration times. The service is expected to enhance appropriate drug use and to prevent medication-related harm among older adults as well as to decrease medication costs, and save nurses' working time in primary care. This doctoral study aimed to investigate the existing evidence on the outcomes of the ADD service, assess the service's initiation process and evaluate its impact on drug use and quality.

A systematic literature review was conducted to summarize the existing evidence on the outcomes of the service in primary care. The initiation process of the ADD service was investigated by surveying community pharmacies offering the service. The service's impact on drug use and quality were investigated using a retrospective cohort study with matched controls applying nationwide register data.

The literature was systematically reviewed until the end of 2019. 20 studies were included, and only two of them were controlled intervention studies exploring the outcomes of ADD in primary care. Consequently, the evidence for ADD's impact on appropriateness and safety of medication use is limited, and lacking on economic outcomes.

When the ADD service was initiated, the medication list was incomplete for more than half (63%) of the patients (n=147). Community pharmacists collected information on patient's medication from multiple sources to reconcile the list. Some type of medication review was conducted for most (96%) of the patients when the ADD service was initiated for them. Most commonly (69% of the patients) it was a prescription review, which is the least comprehensive type of medication reviews. Medication-related therapeutic changes were implemented for almost half (43%) of the patients, and almost all (93%) had technical changes due to the ADD process requirements in their medications while initiating the service.

The retrospective register-based controlled study revealed that ADD users (n=2073) had more starts and discontinuations in their medications compared to their matched controls (n=2073). The results also suggest that drug use was decreased after the ADD service was initiated. When the quality of drug use was assessed by explicit criteria for potentially inappropriate medications for older adults (PIMs by Beers criteria 2012), an improvement was found. However, more complex problems in the drug regimens could not be solved. When the quality of drug use was assessed with more complex

criteria, such as concomitant use of three or more psychotropic drugs, the quality of drug regimens was not improved.

The results of this study imply that medication reconciliation and review need to be integrated into the ADD service procedure as an essential part of it. Both information technology systems and processes in healthcare organisations need to be further developed to ensure that medication records and lists are up-to-date. More comprehensive medication review than prescription review needs to be implemented as a part of the ADD service procedure to ensure rational pharmacotherapy for the ADD users. When municipalities and healthcare providers are purchasing ADD services, medication reconciliation and review need to be included as part of the contract.

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Sinnemäki J, Sihvo S, Isojärvi J, Blom M, Airaksinen M & Mäntylä A: Automated dose dispensing service for primary healthcare patients: a systematic review. Systematic Reviews 2:1, 2013.

II Sinnemäki J, Saastamoinen LK, Hannula S, Peura S & Airaksinen M: Starting an automated dose dispensing service provided by community pharmacies in Finland. International Journal of Clinical Pharmacy 36(2): 345-351, 2014.

III Sinnemäki J, Airaksinen M, Valaste M & Saastamoinen LK: Impact of the automated dose dispensing with medication review on geriatric primary care patients drug use in Finland: a nationwide cohort study with matched controls. Scandinavian Journal of Primary Health Care 35(4): 379-386, 2017.

The publications are referred to in the text by their Roman numerals. The publications were adapted and reprinted with the permission of the copyright holders. This doctoral dissertation also contains previously unpublished data (presented in Chapter 5.3.2).

DEFINITIONS OF THE KEY CONCEPTS

Automated dose dispensing (ADD)
In ADD one or more medicinal products are dispensed into an ADD container or pouch for a patient to take at the particular date and time.[1] Multidose drug dispensing is used as a synonym for ADD.

Adverse drug reaction (ADR)
A response to a drug which is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis or therapy of diseases, or the modification of physiological function.[2,3]

Comprehensive medication review (CMR)
A medication review procedure implemented nationally in Finland requiring accreditation training for pharmacists to conduct it.[4] The procedure is based on collaboration between pharmacists and other healthcare professionals, particularly physicians. CMR includes access to clinical patient data, a home visit with a patient interview, a comprehensive clinical review of all medications in use, a case conference with the physician and documentation to support the process.

Drug-related problem (DRP, also a medication-related problem)
An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[5]

Medication (or medicine or drug)
Medication is pharmaceutical as a product. The words medicine and drug are used as synonyms for medication in this thesis.

Medication adherence
The degree to which use of medication by the patient corresponds with the prescribed regimen.[6]

Medication chart (or list or record)
The complete list of medications, including prescription and over-the-counter medications, herbal and nutritional products taken by the patient.

Medication error
Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer.[7] Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature,

compounding, dispensing, distribution, administration, education, monitoring, and use.

Medication reconciliation
The formal process in which healthcare professionals partner with patients to ensure accurate and complete medication information transfer at interfaces of care.[8,9]

Medication-related harm
Patient harm related to medication. It includes preventable adverse drug events (e.g., due to a medication error or accidental or intentional misuse) and non-preventable adverse drug events (e.g., an adverse drug reaction).

Medication safety
Freedom from accidental injury during the course of medication use; activities to avoid, prevent, or correct adverse drug events which may result from the use of medications.[10]

Medication use process
The multistep process in the use of medications by or for patients, including: prescribing, ordering, storage, dispensing, preparation, administration and/or monitoring.[10]

Patient safety
The absence of preventable harm to a patient and reduction of risk of unnecessary harm associated with healthcare to an acceptable minimum. An acceptable minimum refers to the collective notions of given current knowledge, resources available and the context in which care was delivered weighed against the risk of non-treatment or other treatment.[11]

Pharmacotherapy
In this thesis, pharmacotherapy means treatment of disease (or diseases) with a drug (or drugs).

Polypharmacy
Polypharmacy is 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. This medication use includes over-the-counter, prescription and/or traditional and complementary medicines used by a patient.[12,13]

Potentially inappropriate medication (PIM)
Medications with ineffectiveness or high risk-benefit ratio for a particular individual or group of individuals. [14]

Risk management
Clinical and administrative activities undertaken to identify, evaluate, and reduce the risk of injury to patients.[10]

Transitions of care
The various points where a patient moves to, or returns from, a particular physical location or makes contact with a healthcare professional for the purposes of receiving healthcare.[15]

ABBREVIATIONS

ADD	automated dose dispensing
ADR	adverse drug reaction
ATC	anatomical therapeutic chemical classification system
CI	confidence interval
DDD	defined daily dose
DRP	drug-related problem
EDQM	European Directorate for the Quality of Medicines & Healthcare
GLMM	generalized linear mixed model
GMP	good manufacturing practice
GP	general practitioner
IDU	inappropriate drug use
MAO	monoamine oxidase
MSAH	The Ministry of Social Affairs and Health
n.s.	not significant
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
OTC	over-the-counter
PCNE	Pharmaceutical Care Network Europe
PICO	patients-intervention-comparison-outcomes
PIM	potentially inappropriate medication
RCT	randomized controlled trial
SD	standard deviation
SPDR	Swedish Prescribed Drug Register
SSRI	selective serotonin reuptake inhibitor
SNRI	serotonin and noradrenalin reuptake inhibitor
TTR	time in therapeutic range

1 INTRODUCTION

According to Finland's population forecast, the relative proportion of older adults (65 years or older) is growing. [16] It is well established that morbidity and comorbidity are common in older adults, leading to concomitant use of multiple drugs and elevated risk of the use of potentially inappropriate medications (PIMs).[13,17-22] Drug-related problems (DRPs) and adverse drug reactions (ADRs) are common causes for hospitalization and readmission to hospital in this age group.[23,24]

Strategies for solving challenges related to ensuring appropriate and safe pharmacotherapy for the rapidly growing older adult population have been prioritized in recent medicines policy initiatives in Finland and worldwide. Most recently, the Rational Pharmacotherapy Action Plan by the Ministry of Social Affairs and Health (MSAH) published in 2018 identified challenges in medication use process and also identified how different stakeholders could promote rational pharmacotherapy.[25] Implementation of rational pharmacotherapy was further considered in a memorandum on Points of views on Need for Changes in Medication and Distribution system of Medicines published in 2019 by the MSAH.[26]

During the last decades, Finnish community pharmacies have proactively developed and implemented new services to promote rational pharmacotherapy in primary care.[4,27-31] In addition to patient counselling services, automated dose dispensing services have been established and most widely provided.[30] ADD service was launched in Finland in 2002.[32] In 2007, the MSAH recommended it for municipalities as a method to ensure the safe use of medicines in older adults, along with enhanced multi-professional collaboration and annual medication reviews.[33] The service has also been recommended in the quality recommendation to guarantee a high-quality ageing and effective services for older adults.[34]

Originally the ADD service was developed for hospitals and other institutional settings, and late 1980's it was implemented in primary care in Sweden.[35] ADD is a service in which regularly used medicines are machine-packed into unit-dose pouches for each time of administration.[32,33] In addition to Finland and Sweden, the ADD service is used for primary care patients in Belgium, Denmark, Germany, Norway, and the Netherlands. [36] In Finland, as a part of the service, a medication reconciliation and a medication review are recommended to be performed.[32,33,37]

The ADD service is expected to decrease drug use in general and improve the quality of drug regimens by decreasing inappropriate or unnecessary drug

use.[32-34,37,38] In addition, the service is expected to increase medication adherence, decrease medication administration errors and save the working time of nurses in primary healthcare. Thus, service is expected to enhance patient and medication safety, and decrease medication costs and healthcare utilisation. The ADD service can be seen as a prospective risk management tool for the medication use process.

Although ADD is quite commonly used for geriatric patients with multiple morbidities and medications, there is a limited number of studies on ADD in primary care (see Study I and Chapter 2.4). The impact of the ADD service on the appropriateness of drug use has not been evaluated by using rigorous research methodology. This study aimed to evaluate the ADD process performed for older primary care patients in Finland and its impact on their drug use and its quality. First, the existing evidence on the outcomes of the ADD service was systematically reviewed (Study I). Then the service's initiation process for individual primary care patients was evaluated (Study II). Finally, the service's impact on patients drug use (Study III) and quality (unpublished study) were assessed by using retrospective nationwide register-based data with matched controls.

2 REVIEW OF THE LITERATURE

2.1 THEORY OF HUMAN ERROR: SYSTEMS APPROACH TO RISK MANAGEMENT

In healthcare, processes are complex and mostly performed by multi-professional care teams with a mixture of physicians, nurses, pharmacists and other health professionals. Patients themselves are also active actors in these processes. The same complexity applies to medication use processes performed in various social and healthcare systems and settings. The typical medication use process includes at least the following stages: diagnosis and prescribing, ordering, storage, dispensing, administration of the medicines and monitoring the effects. [39] The process is prone to errors and errors may occur in all the stages of the process. Therefore, errors, for example, medication errors, are a persistent threat to patient safety in healthcare. [39] The Theory of Human Error, established by James Reason in 1990, has been adapted in healthcare to manage these errors and risks. [40,41] According to this theory, errors are inevitable if there are human actions in the processes of the system. The theory has introduced a systems approach to human errors. [40] This approach means that errors occur because of the conditions under which individuals work. Thus, errors can be seen as consequences of a system failure. The traditional approach to errors has blamed individuals involved in an erroneous action, e.g. in patient care, while in the systems approach causes to errors or conditions which lead to errors are seen as weaknesses of the system.

Reason's theory suggests that as human nature cannot be changed, the most important method for preventing errors in the system is to build systemic defences. [40] These defences are illustrated by the 'Swiss Cheese' model (Figure 1). In this model, all the slices of the cheese can be seen as systemic protective defences against failures. The holes in the slices represent weaknesses in the defences. In an optimal process, all the slices are without any holes. Holes in some of the slices, i.e., process phases, would not cause an error if other defences can prevent the error to occur. If the holes are open concurrently in all slices, this may cause an error.

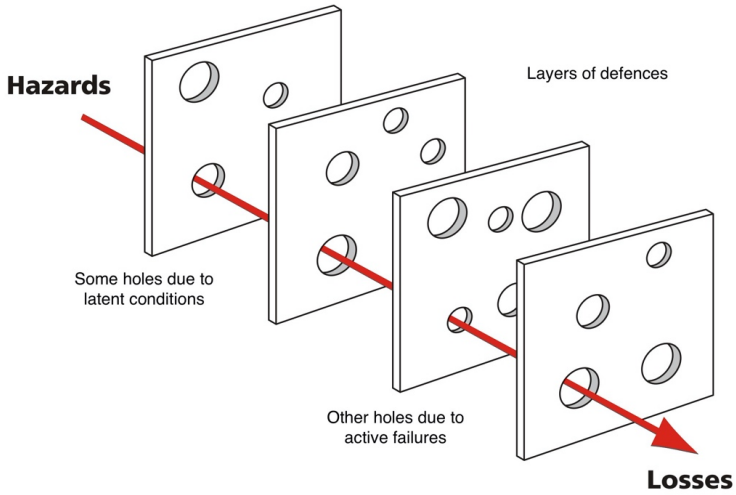

Figure 1. Illustration of Reason's Human Error Theory with a systems approach to error prevention and risk management using the 'Swiss Cheese' model.[40]

However, according to Reason's 'Swiss Cheese' model, there are always holes in the systemic defences. [40] These holes may be caused by active failures and/or by circumstances within the organisation (latent conditions) (Figure 1). Active failures are directly related to how people act in the system/organization. These failures usually have a direct and temporal impact on the systemic defences, and these are difficult to prevent from occurring. On the other hand, latent conditions may have a long-term impact on the defences and risks for errors. Latent conditions could be related, for example, to management decisions. Strategic decisions may enable circumstances prone to errors creating weaknesses to the systemic defences (e.g., how the work environment is designed, how employees competencies are maintained and ensured). Latent conditions can be identified beforehand and, thus, losses caused by these latent conditions are at least partly preventable. It is crucial to evaluate the processes proactively from the risk management point of view to identify latent conditions. The processes should be easily transformed that errors caused by these latent conditions could be prevented.

In the light of Reason's risk management theory, the automated dose dispensing service can be considered as an additional systemic defence in the medication use process for patients having complex medication regimens and multiple medications.[32,33] According to 'Swiss Cheese' model thinking, the ADD service can be placed as one slice (as a systemic protective defence) in the medication use process.

2.2 RISKS AND RISK MANAGEMENT OF DRUG REGIMENS OF OLDER ADULTS

2.2.1 RISKS IN OLDER ADULTS' DRUG REGIMENS

In this chapter, the most common risks in older adults' drug regimens are discussed. Among these is polypharmacy, which also can contribute to other medication risk loads such as drug-drug interactions, anticholinergic and serotonergic load, and use potentially inappropriate medicines (PIMs).[42,43]

Polypharmacy

A recent systematic review found that most commonly polypharmacy is defined as the use of five or more medicines daily.[12] Polypharmacy as such does not necessarily mean inappropriate drug use.[12,44] If the medication regimen is well planned, it is likely to be appropriate. Thus, it has been suggested that polypharmacy as a term should be divided into terms of inappropriate and appropriate polypharmacy.[12]

The prevalence of polypharmacy is found to be high among older adults. The prevalence and factors associated with polypharmacy in long-term primary care facilities have been summarized in a systematic review.[20] The prevalence of polypharmacy (use of 5 or more drugs) varied between the studies from 38.1% to 91.2% while the prevalence of excessive polypharmacy (use of 10 or more drugs) varied from 10.6% to 65.0%. Factors associated with higher polypharmacy rates were recent hospital stays, higher number of prescribers and comorbidities.

In a study performed on nursing homes residents in eight European countries, including Finland, the prevalence of polypharmacy and characteristics related to polypharmacy were investigated.[45] Polypharmacy (concomitant use of 5-9 drugs) was observed in 49.7% of the residents (n=4023) and excessive polypharmacy (concomitant use of 10 or more drugs) in 24.3% of the residents. Polypharmacy was associated with the presence of chronic diseases, depression, pain and gastrointestinal symptoms.

In Finland, a nationwide register-based study found that almost half of all medication expenses in outpatient care cumulated for five per cent of the population.[43,46] Almost 85% of the patients with most pharmaceutical expenditure were using at least five drugs. These patients were older than all drug users. They also had more potentially inappropriate drugs (PIMs) in their regimen than all drug users.

Polypharmacy is common also among patients having ADD service. In previous studies performed on patients using ADD, the mean number of prescribed drugs in use has varied from 9.3 to 13.3. [17,47-50] It is evident that polypharmacy is common among patients using ADD since the service is intended to improve medication management in patients with complex medication regimens.

Excessive anticholinergic load

Anticholinergic drugs are muscarinic receptor antagonists.[51] The number of muscarinic receptors is decreased in older adults' central nervous system. [52] This fact makes older adults more prone to anticholinergic drugs' adverse effects than younger patients. Typical anticholinergic drugs' adverse effects are dry mouth, blurred vision, constipation, urinary retention, postural hypotension, cognitive problems (confusion), and heart rhythm disturbance.[51] Many drugs commonly used in older adults have anticholinergic effects. Among these drugs are, e.g., Parkinson's disease drugs, drugs for the treatment of incontinence, tricyclic antidepressants, sedative antihistamines, and muscle relaxants.[53,54]

The prevalence of anticholinergic drug use varies among older adults. In a study performed in Germany for primary care patients (≥75 years, n=2605) it was found that 37% of the patients used the anticholinergic drug at least one point during 4.5 years study period.[55] In two studies from France it was found that 9.2-13.7% of the older adults (>60 and >70 years) continuously used anticholinergic drugs. [56,57] In a large-scale register-based study from the United States, it was found that 9.56% of older adults (≥65 years) used potentially inappropriate anticholinergic medications in 2009-2010.[58] In Finland, a study involving older people (>65 years) living in nursing homes and assisted living facilities showed that 51% used at least one drug with anticholinergic effects. [59] Another Finnish study involving aged (≥65 years) community-dwelling primary care patients with diabetes found the prevalence of anticholinergic drug use to be 8.9%.[60]

In studies performed on patients using ADD, the prevalence of anticholinergic drug use has found to be high.[17,47-49] The prevalence has varied from 12.8% to 20.3% between studies. In a large-scale register study from Sweden, the prevalence of anticholinergic drug use was 15.3% among ADD users while prevalence was 4.9% among patients not using ADD.[17]

It is established that the use of anticholinergic drugs impairs cognition of older adult patients. [56,57,61] There is also evidence that higher cumulative anticholinergic use is associated with an increased risk of dementia.[62,63] The use of anticholinergics is also associated with an increased risk of falls or fractures in older patients.[64]

Excessive psychotropic and sedative load

Many drugs, e.g., most antidepressants, antipsychotics, benzodiazepines and their derivatives, opioids, and spasmolytics, Parkinson's disease and antiepilepsy medicines, have sedative effects on patients.[53,54] Older adults are sensitive to the effects of sedative drugs because of physiological changes in their central nervous system and body functions, such as changes in the metabolism of the brain tissue. [52,65]

The use and long-term use of sedative drugs, especially benzodiazepines and their derivatives, is common among older adults.[66] In a large-scale register study performed in Sweden it was found that at least 1.5% of Swedes 75 years or older used long-acting benzodiazepines.[21] The use was even more common among 85 years or older (1.9-2.6 %). In the same study, it was found that the prevalence of use of three or more psychotropic drugs varied from 2.5 to 3.4 % among aged. In a national study from Finland, it was found that the prevalence of long-term benzodiazepine use among 65 years or older was 7.6%.[66] A systematic review reveals that 3-14% of the home-dwelling Finnish older adults used antipsychotics.[67] The use of psychotropics and long-acting benzodiazepines among patients using ADD has also been studied in Sweden.[17,47-49] The prevalence of concomitant use of three or more psychotropics (16.1% to 38.6%) as well as the prevalence of use of long-acting benzodiazepines (8.8% to 15.5%) has been found to be high.

The proportion of adipose tissue increase when people get older.[65] As a consequence, the distribution volume of the benzodiazepines is expanded, and half-life becomes longer. The risk for long-acting benzodiazepines' cumulation is high.[65,68] There is evidence that long-term use of benzodiazepines in older adults is related to the prolonged impairment of cognitive function.[69] The use and long-term use of benzodiazepines and related drugs have also been shown to be linked with daytime and night-time symptoms, such as dizziness, inability to sleep after waking at night and tiredness.[70] The adverse effects of these drugs might cause these symptoms. A systematic review also found that exposure to benzodiazepines is associated with a higher risk for falls in older adults.[71]

Other sedatives than benzodiazepines may also have severe adverse effects for older users. Common antipsychotics' adverse effects in older adults are confusion, cognitive and functional decline, sedation, hypotension, orthostasis, dizziness, falls, urinary incontinence, and increased risk of urinary infections.[72] According to a meta-analysis, most common adverse effects of opioids among older adults included constipation, nausea, and dizziness.[73] Because of increased evidence on their harmful effects on older adults, even in

short-term, but particularly in long-term use, some antipsychotics and benzodiazepines are classified as PIMs.[74,75]

Serotonergic load

The serotonin system is affected by many drugs. Among these drugs are selective serotonin reuptake inhibitors (SSRI-drugs), serotonin and noradrenaline reuptake inhibitors (SNRI-drugs), monoamine oxidase inhibitors (MAO inhibitors), tricyclic antidepressants, and some opioids.[54] Cumulation of these drugs is possible among older adults since most of them are fat-soluble, and thus, the distribution volume is expanded, and half-life becomes longer.[76] Ageing also affects cholinergic and dopaminergic activity and decreases the number of serotonergic receptors in the central nervous system. [52,77] Thus, older adults are sensitive to the adverse effects of these drugs.

The most severe adverse effect of serotonergic drugs is serotonin syndrome. [78] It is a drug-induced toxidrome associated with increased serotonergic activity in both the peripheral and central nervous systems. The symptoms of the syndrome are neuromuscular abnormalities, autonomic hyperactivity, and mental state changes. The combination of a MAO inhibitor with serotonergic drugs is especially dangerous and may lead to the most severe form of the syndrome, and occasionally to death.

Antidepressant drug use is also associated with significantly increased risks of falls, fractures, and upper gastrointestinal bleeding compared to the situation when these drugs were not used.[79]

Drug-drug interactions

Older adults are more prone to drug-drug interactions than younger patients.[80] When drug interactions are assessed, many factors need to be considered, such as age-related changes in pharmacokinetics and pharmacodynamics, frailty, interindividual variability, reduced homeostatic mechanisms, and psychosocial issues. There is also evidence that polypharmacy is a significant predictor of adverse drug reactions induced by drug-drug interactions.[42]

The prevalence of potential drug-drug interactions is high among older adults. In a register study from Sweden, it was found that the prevalence of the potentially serious (class D) drug-drug interactions among aged (≥75, studied in five year age groups) varied from 1.6% to 2.1%.[21] The prevalence of class C (may change the effects of the drugs but can be managed by adjusting the dosage) drug-drug interactions varied from 11.9% to 15.7%. Both class C and class D interactions were most prevalent in patients aged 85–89 years. In

studies performed on patients using ADD, the prevalence of class D drug-drug interactions has been found to be remarkably higher (7.6% to 12.1%) than in the study mentioned above.[17,47-49]

A study from Finland performed on residents 65 years or older in primary care assisted living facilities found that 5.9% of the residents were at risk for class D drug-drug interactions.[81] Drug-drug interactions were associated with a higher number of drugs. Another study from Finland found that methotrexate and warfarin had the highest risk of causing potentially serious (class D) interactions in outpatient care.[29] The interactions were most common between methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin and NSAIDs.

2.2.2 RISK MANAGEMENT OF OLDER ADULTS' DRUG REGIMENS

Different types of risk management tools have been developed to identify the risks in older adults' drug regimens. Among these tools are different types of criteria for potentially inappropriate medications (PIMs) that can 1) prevent prescribing or using medicines that can be harmful, or can 2) assist in identifying these risk drugs in patients' drug regimens, e.g., while reconciling and reviewing medications. Currently, these criteria have also been integrated into the electronic medication risk management databases to facilitate the use of the criteria in clinical practice.

Considering the ADD service in Finland, a medication reconciliation and review are recommended to be conducted as a part of the ADD service.[32,33] Thus, medication reconciliation and medication review procedures are discussed in this chapter.

Criteria to identify potentially inappropriate medicines in older adults' drug regimens

One of the first criteria to identify inappropriate drugs on older adults drug regimens was the Beers criteria published in 1991 in the United States. [82] Since then, numerous other criteria have been derived from Beers criteria or developed by using other resources.[83]

Beers criteria

The first version of the Beers criteria was composed by using the Delphi method, and it was targeted to nursing home patients.[82] In 1997 the criteria were expanded to concern also outpatient care patients.[84] The Beers criteria have been updated in 2003, 2012, 2015, and 2019.[75]

The American Geriatrics Society published the latest update of Beers criteria.[75] The Beers Criteria is an explicit list that contains potentially inappropriate medications (PIMs). The Beers criteria are widely used when the safety of prescribing medications for older adults is consulted. The criteria are also used in the geriatric clinical care, education, research and in the development of quality indicators.

The Beers criteria define 1) potentially inappropriate medications and medicine classes to be entirely avoided in older adults, 2) potentially inappropriate medications and medicine classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate, and 3) medications to be used with caution in older adults.[75] These three categories were first published in the update from 2012 and were updated in the latest version of the criteria.[85]

New to the Beers criteria published in 2015 were lists of drugs that should be avoided or have their dose adjusted based on the individual's kidney function and selected drug-drug interactions documented to be associated with harms in older adults.[68,75] The quality of evidence and strength of recommendation for each criterion was also assessed for the first time in the version published 2015. The Beers criteria apply to all older adults (≥65 years) with the exclusion of those in palliative and hospital care.

However, these Beers lists are not intended to be comprehensive since such lists would be too extensive. Furthermore, the Beers lists reflect medicines used in the US. Thus, it needs to be adopted if used in other countries. [22]

Laroche criteria

The Laroche criteria were published in 2007 by French researchers. [86] The criteria were compiled using the Delphi method. The criteria are based on the Beers criteria, Canadian criteria, and French recommendations on older adults' drug regimens. As a result, the final Laroche list contained 34 criteria: 29 medications or medication classes to be avoided in all older people and five criteria related to medications that should be avoided in specific medical conditions. In most cases, drugs were considered inappropriate as their benefit-to-risk ratio was unfavourable and/or drugs were considered with questionable efficacy. Inclusion reasons for the drugs were also published as well as alternative drug treatments. The Laroche criteria apply to people 75 years of age and older.

STOPP/START criteria

The first version of the Irish criteria for PIMs called STOPP (Screening Tool of Older Persons' Prescriptions) and criteria for potentially appropriate,

indicated drugs called START (Screening Tool to Alert doctors to Right, i.e., appropriate, indicated Treatment) was published in 2008.[87] Also these criteria were assembled by the Delphi method. STOPP includes 65 clinically significant criteria for potentially inappropriate prescribing in older people (≥65) and START 22 evidence-based prescribing indicators for commonly encountered diseases in older people.

The latest update of the STOPP/START criteria was published in 2014.[88] Altogether 114 criteria after two Delphi validation rounds were included, i.e., 80 STOPP criteria and 34 START criteria. The number of items in the STOPP/START criteria was increased by 31% compared to the first version of the criteria.

Meds75+ (Lääke75+) database

The Meds75+ is a Finnish database of PIMS maintained by the Finnish Medicines Agency.[74] The database is based on multidisciplinary clinical consensus and information derived from Beers, STOPP/START and Laroche criteria. The database contains almost 500 drugs that are classified into categories A, B, C and D according to their suitability to geriatric use. The purpose of the database is to support clinical decision-making concerning pharmacotherapy for older adults (≥75 years) and to improve medication safety in primary care. The database is intended to be used by physicians and other healthcare professionals. The database was recently integrated as a part of the more extensive Finnish database (Terveysportti) which is targeted to physicians and other healthcare professionals.

Medication reconciliation

Unintended discrepancies in patients' medication records are common and could cause medication errors, and thus harm to patients.[89] Discrepancies in medication records are also common in Finland. [90] Medication reconciliation is a recommended procedure to update medication lists.[9] Medication reconciliation has been defined by the Institute for Healthcare Improvement IHI (US) as follows: "Reconciliation is a process of identifying the most accurate list of all medications a patient is taking — including name, dosage, frequency, and route — and using this list to provide correct medications for patients anywhere within the healthcare system". [9]

Pharmacist involvement in the medication reconciliation process has been found to be effective in systematic reviews.[91,92] A systematic review assessing the impact of the medication reconciliation in the community setting found that a pharmacist can identify and resolve discrepancies while conducting medication reconciliation. [93] However, the results of this review did not support a reduction in readmission rates or reduction in healthcare utilisation

(e.g., emergency department attendance and GP appointments). Other systematic reviews showed a reduction in medication discrepancies, potential adverse drug events, and adverse drug events after the medication reconciliation.[91,92] Medication reconciliation should primarily be targeted to a high-risk patient population.[94]

The evidence of the effectiveness of medication reconciliation processes is inconsistent. [91,94,95] Medication reconciliation may not reduce post-discharge hospital utilization but might reduce utilization when combined with interventions aimed at improving care transitions.[91,94] Another systematic review concluded that a pharmacist-led medication reconciliation programme at hospital transitions might decrease adverse drug events related to hospital revisits, all-cause readmissions and emergency department visits.[95]

Collaborative medication reviews

Medication reconciliation procedures are often combined with medication reviews. Reviewing of medications is a part of physicians daily routines when assessing treatment decisions. Currently, practices in which pharmacists reconcile and review the medications of the patients in collaborative care teams are more common.[31,96] Medication review has been defined by the Pharmaceutical Care Network Europe (PCNE) in 2017: "Medication review is a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions.".[97] Different types of collaborative medication review procedures have been developed that vary in the comprehensiveness of the review.[4,96,98,99] According to the UK guideline, medication reviews can be classified into the following three types: prescription reviews, concordance and compliance reviews, and clinical medication reviews (Table 1). [100,101]

Table 1. Characteristics of the three types of medication reviews according to the British guideline by Clyne et al., adapted.[100,101]

	Purpose	Patient involvement	Access to patients' clinical data	Includes all prescription medicines	Includes prescription, OTC and complementary medicines	Review of medicine and/or condition
Type 1: Prescription review	Address technical issues relating to the prescription, e.g., anomalies, changed items, cost-effectiveness	No*	Possibly**	Possibly***	No	Medicines
Type 2: Concordance and compliance review	Address issues relating to the patient's medicine- taking behaviour	Usually*	Possibly**	Yes	Yes	Medicines use
Type 3: Clinical medication review	Address issues relating to the patient's use of medicines in the context of their clinical condition	Yes	Yes	Yes	Yes	Medicines and condition

*Any resulting changes to prescribed medicines must involve the patient/carer. **Medicines use review by community pharmacist may not include access to patient's clinical notes. ***A prescription review may relate to one therapeutic area only rather than all prescribed medicines. OTC = over-the-counter.

The type 1 review, the prescription review, is the least comprehensive of the reviews.[100] It can be performed without the presence of the patient. This review might reveal the need for a more comprehensive medication review. The concordance and compliance review (type 2) usually involves a patient.[100] In this review, exceptionally patient's medicine taking, beliefs about medicines and ability and intent to take medicines is evaluated. The aim is to support patients' self-care. The most comprehensive medication review is clinical medication review (type 3). [100] This review is performed with a patient. This review has a more holistic approach to patient's condition taking account also patient's clinical data. The review is usually performed by a prescriber or by a specially trained practitioner (e.g., an accredited pharmacist).

In Australia Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) programs have been implemented.[99] In the United States, collaborative medication reviews are implemented under the concept of medication therapy management (MTM).[98] The MTM procedure highlights a patient-centeredness. In Finland, the first collaborative medication review procedure was a comprehensive medication review (CMR) procedure for older adults in primary care.[4,102] This is a clinical medication review requiring a specially trained pharmacist to conduct it.[102,103] The CMR consist of four action phases: a patient interview, structured medication review process, and a multidisciplinary case conference to decide on actions and follow up (Figure 2).[4,102]

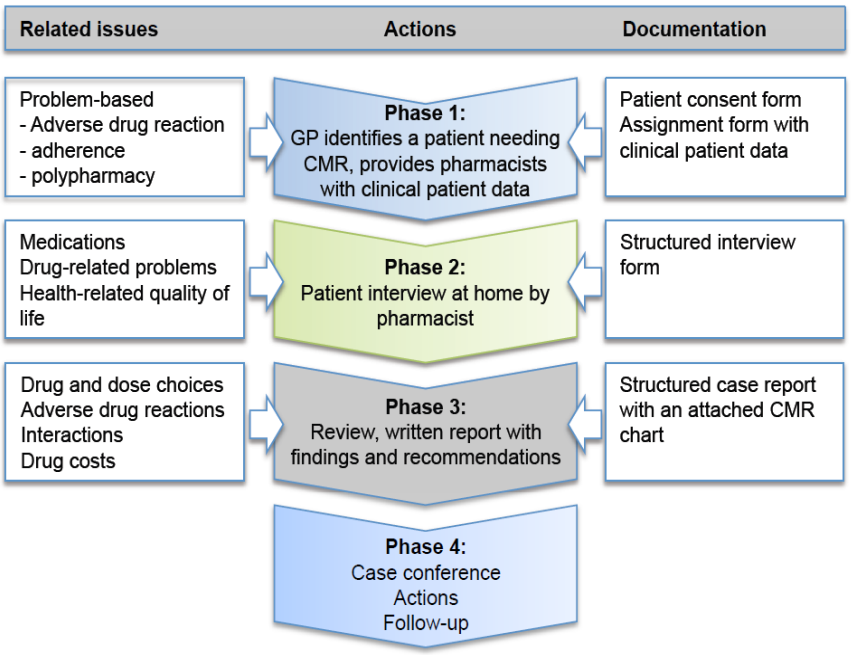

Figure 2. Phases of the comprehensive medication review (CMR) procedure in Finland.[4]

The potential risks recommended to be covered in the CMR are presented in Figure 3.[4] These risks are divided into the following four dimensions: 1) ageing and safety, 2) co-morbidities, 3) polypharmacy, and 4) adherence.

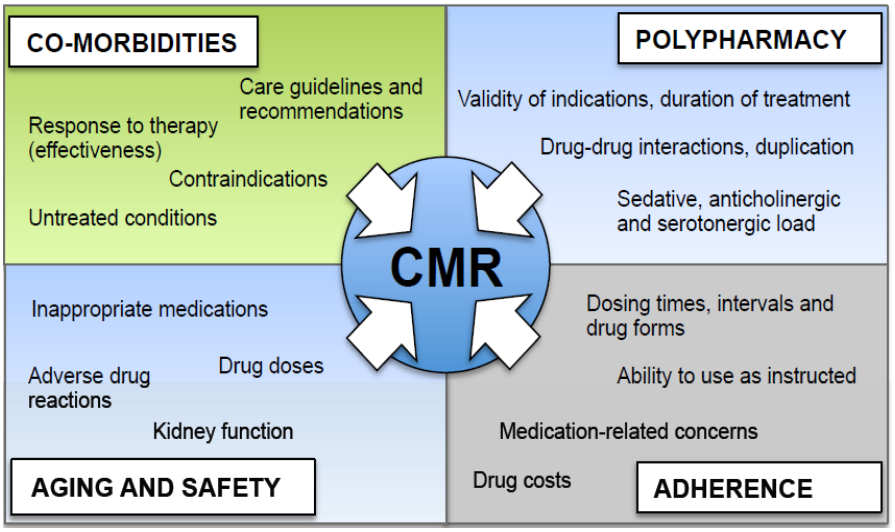

Figure 3. The four dimensions of potential risks recommended to be covered in the comprehensive medication review (CMR) procedure.[4]

CMR procedure developed in Finland in mid-2000s has evolved to diversified procedures performed in various settings, [28,31] although their large-scale breakthrough has not yet happened.[30] However, different types of medication review procedures, mostly CMR procedures, are available and implemented in use and targeted to older adults in primary care.[31]

There is cumulative evidence on effectiveness of collaborative medication review practices. [104-106] A systematic review evaluated pharmacist led interventions on potentially inappropriate prescribing.[104] Only randomised controlled trials or quasi-randomised studies were included in this review. The conclusion was that pharmacist led interventions may improve the appropriateness of prescribing. Similar conclusion was made in another systematic review.[105] The third systematic review aimed at assessing the impact of medication reviews.[106] The research has concluded that pharmacist led medication reviews appear to improve the quality of medication use among older adults. However, all three systematic reviews also concluded that the quality of evidence is still weak.[104-106] In addition to these studies, Kallio et al. have published a systematic review investigating community pharmacists contributions to medication reviews.[107] The study indicated that community pharmacists contribution could be enhanced in medication review procedures to a more holistic contribution than just identifying DRPs.

In Finland, there have been three recent implementation studies that have assessed the impact of collaborative medication reviews on patient outcomes. [28,29,108,109] The project in Lohja was focused on enhancing coordination between home care and community pharmacies in medication management.[28] The action research method was applied to develop a triage procedure for reviewing medications of home care clients.[28] The procedure involved home care nurses and practical nurses, as well as community pharmacists in conducting the preliminary review of each client's medication and select the cases that needed to be discussed with the physician for further actions. The impact of the triage procedure was evaluated in a randomised control trial (RCT) that focused on reducing medication risks as an outcome.[110] At baseline, clinically significant medication-related risks were typical among home care clients in both groups (study and control). The results indicated a tendency for effectiveness, particularly in optimizing the use of central nervous system medication, such as benzodiazepines. It is noteworthy that these home care clients had their medicines dispensed by ADD.

Another implementation study also developed a collaborative medication review procedure for home care clients.[108,109] A structured medication review was performed by an interprofessional team consisting of a pharmacist, a physician and home care service's nurse. All pharmacists were qualified to perform the procedure. The baseline findings of this study were consistent with the findings in Lohja home care services: clinically significant

medication-related risks were common.[108,110] In the RCT conducted impact on medication, functional capacity, quality of life and use of health and home care services were assessed. The results imply there was a positive influence on the content and the risks associated with pharmacotherapy. Any effects were not found on other outcome measures. However, the researchers concluded that the collaborative medication review procedure could be used for promoting rational pharmacotherapy in home care.

The third implementation study on CMR practices in primary care in Finland focused on how critical patient involvement is in CMR procedure and in identifying DRPs.[111] The results indicated the importance of interviewing the patient as part of the procedure. Without the interview more than 80% of the DRPs would have been missed, among these poor therapy control, nonoptimal drug use, and intentional or unintentional nonadherence.

In conclusion, there is growing evidence that collaborative medication reviews should be integrated as a routine practice in the medication use process in primary care and other care settings where medicines are used as part of the treatment. Integration of CMR in the care process and medication use process is crucial for its effectiveness.[112] Older primary care outpatients, even those having home care support and ADD service seem to form a group of high-risk patients who have commonly clinically significant risks in their medications that require attention.[17,49,108,110,111,113-116] A Dutch study indicated that a medication review decreased the number of drug-related problems (DRPs) when conducted to ADD patients.[117] The researchers recommended that all patients with ADD should have a comprehensive medication review conducted jointly with a prescriber and a pharmacist.

2.3 AUTOMATED DOSE DISPENSING SERVICE PROVIDED BY COMMUNITY PHARMACIES

In ADD one or more medicines are dispensed into an ADD pouch or container.[1] These are produced by an automated process using special equipment. Each pouch or container contains regularly used medicines that are intended to be administered to a patient at the same time. The ADD service has been suggested to decrease drug use by reducing drug waste, increasing medication adherence, improving the quality of drug regimens by decreasing inappropriate or unnecessary drug use.[32-34,38,40] In addition, the service is expected to decrease medication administration errors and save the working time of nurses in the primary healthcare.

In Europe, ADD is used for primary healthcare patients in Belgium, Denmark, Finland, Germany, Norway, Sweden, and the Netherlands.[36] ADD was launched in primary care in Sweden in the 1980s.[35] Until then, community

pharmacies were manually repackaging medicines in multi-dose packages. The rationale for the service was to increase safety and save time. In Finland, ADD was launched in 2002 by the Association of Finnish Pharmacies.[32]

This literature review provides an overview of the ADD service in Finland, Sweden and the Netherlands. Sweden and the Netherlands were selected as examples since ADD is widely used among older adults in these countries.[35,36] Most of the studies on ADD were also performed in these countries (see chapter 2.4.1 and Study I). The information on practices regarding ADD in Sweden and the Netherlands was challenging to find using literature review as a method. Thus, the procedures applied in ADD in different countries should be benchmarked using proper study methods (e.g., a survey).

ADD in Sweden

In 2018 there were approximately 200 000 patients receiving medicines via ADD in Sweden.[36] Of those patients, about 100 000 were living at home and about 100 000 were nursing home residents. The majority of the home dwelling ADD users were assisted with delivery of medicines by home care staff. [35] A majority of ADD users are older people, e.g., in 2011, about 80% of them were 65 years or older. [35]

The ADD service is reimbursed and covered by the Swedish Pharmacy Benefit.[35] The service can only be prescribed by a physician, most often following the suggestion or recommendation by a municipal district nurse. The patient's complete medicine regimen including both prescription and OTC medicines is transferred to the national prescribing database. For long-term therapies, prescriptions are valid for 12 months, after which they need to be renewed. Usually the ADD pouches are filled for two weeks demand at a time.[118]

Until 2013, only National Corporation of Swedish Pharmacies offered ADD.[35] Since the spring 2013, other companies in Sweden also have offered this service. The Swedish Medicinal Products Agency established a guideline on dose dispensing in 2010.[119] In this guideline, detailed standards for the ADD sites and operations are set. However, national patient care recommendations (e.g., how ADD is started for patients and if it includes any interventions to ensure appropriate drug use) were not found in the literature review.

ADD in the Netherlands

In the Netherlands, the ADD service is predominantly used as a dosing aid in primary care.[120] The service is widely used, there were 360,000 ADD users in 2011.[121] Approximately 12% of the people over 65 years old used the ADD service in 2018.[122] One reason for this high number of ADD users is the fact

that the legislation does not allow home care employees to manage their clients' medications.

Hospital pharmacies are generally responsible for dispensing medicines for both hospital wards and nursing homes.[123] ADD is especially used in nursing homes to support the nurses in the administration of medicines. The ADD pouch production can be located in the hospital itself or community pharmacies. Most of the community pharmacies purchase ADD service from a pharmacy that specialises in ADD (ADD supply units). The community pharmacists are responsible to entering the prescriptions into the pharmacy information system, and subsequently transmitting the ADD order electronically to the ADD supplier. According to the order, the supplier fills the ADD pouches. The dispensing pharmacies are responsible for the clinical and accuracy checks of medications, not ADD supply units.[36] Usually the ADD pouches are filled for one week's use at a time.[120]

Hospital pharmacies dispense ADD pouches to the nursing homes and nurses administer the medicines to the patients.[123] Community pharmacies dispense the ADD pouches directly to patients and counsel them about the medicine use and how to use the ADD pouches. Home care nurses may help some of the home dwelling patients with the ADD pouches.

In the Netherlands, the ADD service is more expensive compared to manual dispensing.[124] Thus, ADD is targeted to patients who have a decreased medication management capacity. The ADD service is only reimbursed to patients for whom the general practitioner has decided to start the service.

In this literature review any recommendations on patient care were not found.

ADD in Finland

Finland had 54 500 patients using the ADD service at the end of the year 2018. The number of patients using the service has continuously increased. The number of patients using the service was 20 000 at the end of 2012 and 49 500 at the end of 2016. Most of the ADD service users are home-care clients or nursing home residents. The Ministry of Social Affairs and Health has recommended the ADD service for older primary care patients to ensure safe medication in its guidance to municipalities in 2007. [33] In 2016, the Ministry published guidelines for providing the ADD service.[37]

Service fee of ADD

Healthcare services in Finland are publicly funded and arranged by the municipalities.[125] Municipalities may procure healthcare services from privately-owned healthcare providers. Medicine supply and related

pharmaceutical services for outpatients are mainly provided by community pharmacies. Most municipalities and privately-owned healthcare providers procure the ADD service from the community pharmacies. The ADD service is more commonly put out to tender to buy the service at a competitive price.[126] [37] In these competitive tenders both qualitative (e.g., level of medication review) and quantitative (e.g., service fee) conditions may be set and the pharmacies could set the price for the ADD service freely.

Since 2006, the ADD service fee has been partly reimbursed by National Health Insurance that covers the entire population.[38] The service fee is only reimbursed for home-dwelling aged patients (≥75 years) using six or more reimbursable prescription medicines that are suitable for ADD. In addition, the ADD service needs to be prescribed by the physician and the patient's drug regimen needs to be reviewed by the physician before initiating the service. The public insurance does not cover the service fee if the patient receives drug distribution services by home care services arranged by the municipality or by the privately-owned healthcare provider. In these cases, the service fee is covered by the municipality or the healthcare provider.

Production of the ADD pouches

In Finland, only community pharmacies or hospital pharmacies can manufacture dose dispensed pouches or similar packages by a machine.[127] It is compared to the manufacture of medicines, and thus, the production must fulfil good manufacturing practice (GMP) requirements, if applicable. Before a pharmacy could start to dose dispense, a licence issued by the Finnish Medicines Agency is required. To get a licence, the pharmacy must have personnel in place to manufacture medicines, an appropriate manufacturing site and equipment. The licenced dose dispensing pharmacies are inspected regularly by the Finnish Medicines Agency.

Community pharmacies in Finland are allowed to procure dose dispensed medicines from the licenced dose dispensing community pharmacies.[127] At the end of year 2019, there were four community pharmacies licenced to manufacture dose-dispensed pouches or similar packages (unpublished data received from the Finnish Medicines Agency). The ADD service is delivered nationally through community pharmacies that procure ADD from these providers. At the end of 2018, 493 out of the 616 community pharmacies (80%) provided the ADD service (unpublished data received from the Finnish Medicines Agency).

National guidelines on ADD

In 2016, the Ministry of Social Affairs and Health published guideline on good practices on ADD.[37] The aim of the guideline was to implement a nationally

standard procedure for the ADD service to ensure that patients are in an equal position in terms ADD's influence on their medication process. The guideline is primarily targeted to social and healthcare institutions (for nurses and practical nurses), community pharmacies (pharmacists) and primary healthcare (general practitioners, home care services' personnel) as a guide for 'best practices'.

The guideline was drawn up in collaboration with the national authorities.[37] Social and healthcare stakeholders were consulted before the guideline was published. The studies of this thesis (studies I and II) and international studies on ADD were utilised while the guideline was composed. In this guideline the whole process of the ADD service was described. The most crucial part of the guideline from the patient care point of view is the medication review conducted when the ADD service is initiated.

Under the guidelines, the medication review is to be performed by a physician in the multiprofessional collaboration (Table 2).[37] A nurse and a pharmacist participate in this process. According to the recommendations, a crucial phase of the collaborative medication review process is collection of patient information (Table 3 and Figure 4). In this phase, all crucial information is gathered to conduct the medication review. The pharmacist is responsible to conduct the review prior the case conference. While conducting the review, the pharmacist needs to consider patient's age and diagnosis. In addition to these factors, clinically significant drug-drug interactions, harmful medication loads, and medicines recommended to be avoided in older adults (PIMs) need to be identified (Table 2). After the pharmacist has conducted the medication review, a multiprofessional case conference is recommended (Figure 4). All final decisions regarding patients' medications are made by the physician. Finally, all actions that needs to be taken to implement in the patient's medication plan need to be documented. The medication review is recommended to be performed regularly at least once a year, not only as a part of the initiation process.

Table 2. Different healthcare professionals responsibilities in medication review process as a part of the initiation of the ADD service.[37]

Function	Healthcare professional responsible		
	Nurse	***Pharmacist***	***Physician***
Monitor effects of the pharmacotherapy	**x**		**x**
Medication review (the following aspects need to be checked): • drug doses • administration times • duplications • drug-drug interactions • harmful medication loads • untreated conditions • validity of indications • drugs avoided for older adults (PIMs)		**x**	
Organize the case conference	**x**		
Participate in the case conference	**x**	**x**	**x**
Final decision on patient's pharmacotherapy and which medicines are dose dispensed			**x**
Decide when patient is enrolled to ADD	**x**		
Compile the complete medication list	**x**		
Document the medication review process	**x**		**x**

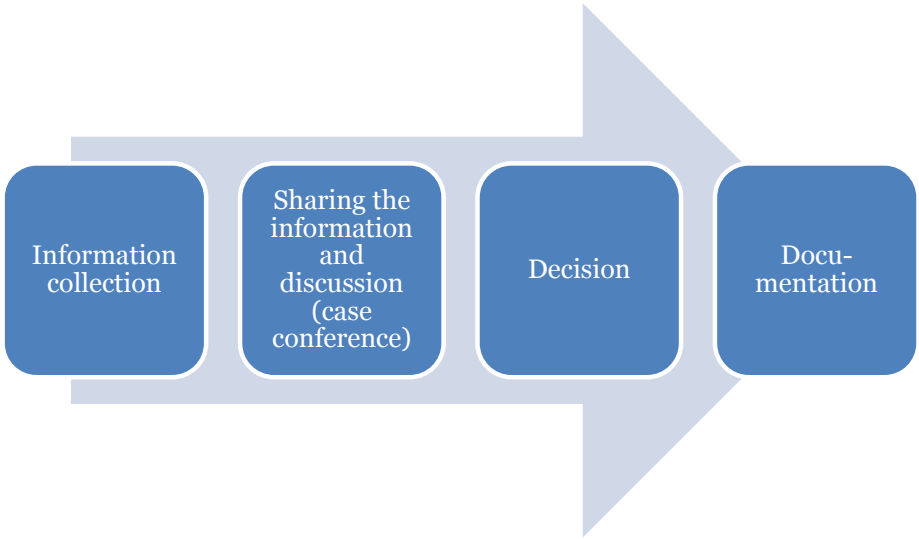

Figure 4. Medication review process for the ADD patients according to the Finnish guideline.[37]

Table 3. Responsibilities of different stakeholders in the information collection phase.[37]

Nurse	Physician	Pharmacist
• Compile complete medication list (patient interview is recommended, and if needed, a pharmacist consulted) • Collect information on patient's condition and health related measurements • Evaluate how the patient copes with medications	• Collect diagnoses and indications of the medicines • Assess the severity of the diseases • Assess the doses of the medicines	• Conduct review based on information gathered by a nurse and a physician

In Finland dose dispensed medicines are usually dispensed in two week intervals.[37] A community pharmacy dispensing the medicines to the patient orders dose dispensed medicines from a dose dispensing pharmacy (Figure 5). Usually orders are done couple of days prior to dispensing of the medicines. Patients' care units are advised to deliver information on possible changes in the patients' drug regimens before the order. Changes need to be based on a physician's prescription. The order phase is a critical point in the process from the medication safety point of view. In this phase, the medicines dispensed via ADD are settled (according to the physician's decision) and the dispensing

times for the medicines are determined (e.g., how many pouches per day are needed).

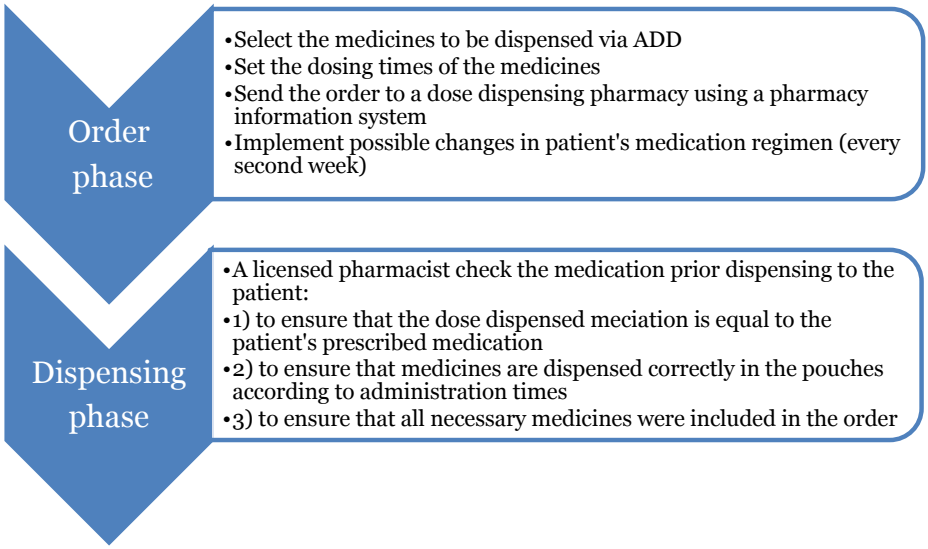

Figure 5. The order and dispensing phases of ADD in community pharmacies in Finland.[37,128]

Another critical point in the process is the dispensing phase of the medicines (Figure 5). The procedures of this phase is determined more detailed in the medication dispensing order (in Finnish: Fimean määräys lääkkeiden toimittamisesta) published by the Finnish Medicines Agency.[128] The latest update of this order was published in 2017. Pharmacists are obliged to comply medication dispensing order when dispensing medicines from a community pharmacy. In this order, preconditions are set when ADD medicines are dispensed from the community pharmacy. According to the order, medicines must be checked by a licensed pharmacist (bachelor's or master's degree) prior dispensing them. In this check, the pharmacist needs to verify that the medicines in the dose dispensing pouches (or similar) are equal to the patient's prescribed medication and that medicines are dispensed correctly in the pouches according to administration times. In addition, the pharmacy dispensing the medicines needs to ascertain that medicines are ordered correctly from a dose dispensing pharmacy and that all medicines necessary for a patient are not missing from the order. All other regulations regarding dispensing of the medicines must comply when dose dispensed medicines are dispensed from a community pharmacy. These include e.g. medication counselling.

Council of Europe guidelines on ADD

The European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe has published guidelines on best practices for the

ADD process, and care and safety of patients in 2018.[1] However, these guidelines mainly offer detailed standards for the ADD sites and operations, and only few recommendations on patient care. These patient care recommendations include the review of the patients' medication therapies but detailed instructions are not included. It is stated in the guidelines that since these activities are dependent on the healthcare system of the present country, the guidelines cannot not present the process in detail. However, in the guideline multidisciplinary procedures to review and manage all of the patient's medications regularly and systematically are acknowledged.

2.4 STUDIES SINCE 2012 ON AUTOMATED DOSE DISPENSING PROVIDED BY COMMUNITY PHARMACIES

2.4.1 LITERATURE REVIEW

The literature review for this chapter was performed using a similar method than the systematic review presented in the empirical part of this thesis (Study I). Studies published within the period from April 2012 to December 2019 were included (studies published prior to April 2012 were included in the study I). The descriptions and results of the studies are presented in Table 4.

Altogether 13 studies were found.[35,113-116,118,120-124,129,130] Three of the studies included were cohort studies,[114,116,129] and only one of them was controlled.[129] Six studies were descriptive studies on either ADD as a process or patient drug use.[113,115,120,121,123,124] Four of the studies were descriptive studies about ADD users' or healthcare professionals' perceptions and experiences with ADD.[35,118,122,130]

Table 4. Description and results of the studies on automated dose dispensing (ADD) in primary healthcare published between April 2012 and December 2019 (n=13).

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Controlled cohort study (n=1)				
van Rein et al.,[129] 2017, the Netherlands A retrospective controlled cohort study	To investigate the impact of ADD on adherence to vitamin K antagonist treatment	Study group: 83 ADD users who were non-adherent to vitamin K antagonist treatment. Control group: 333 non-ADD patients matched on age, sex, medication and adherence. Data collection: patients were chosen and Time in Therapeutic Range (TTR) data was collected from Leiden Anticoagulation Clinic.	TTR was calculated between two measured INRs (international normalized ratio) 6 months before ADD (baseline, reference) and every month after ADD initiation (6 months period).	The TTR of the study group had a 10% (95%CI 2;19) higher TTR increase after one month of the initiation of ADD when compared to control group. After four months the difference in TTR increase (3%) was not statistically significant (95%CI -2;9) between the groups.
Uncontrolled cohort studies (n=2)				
Bobrova et al.,[114] 2019, Finland A retrospective cohort study	To investigate ADD users' quality of drug use at the initiation phase of the service and 6 months after the initiation	Participants: 208 ADD users (≥65 years) enrolled to the service during September 2015. Data collection: medication lists were collected from dose-dispensing unit's records at 0 and 6 months.	Use of potentially inappropriate medications (PIM) as listed in the European Union EU(7)-PIM-list. Clinically significant drug-drug interactions according to the Inxbase (category D). The number of dose dispensed drugs in use.	The proportion of the patients exposed to clinically significant PIMs was higher after 6 months (59% vs. 64%, $p<0.01$). At least one clinically significant drug-drug interaction (category D) was identified in 2.4% of the patients, proportion was the same after 6 months (not statistically tested). The number of used drugs increased for 61% of the patients for six months (at baseline 5.9 drugs, not statistically tested).

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Wallerstedt et al.,[116] 2013, Sweden A retrospective cohort study	To investigate ADD users' quality of drug use during the 3 months before and the 3 months after ADD was initiated	Participants: all patients ≥65 years of age, living in Västra Götaland who entered to ADD between 1st July 2006 and 30th June 2010 (n=30 922). Data collection: data on prescribed drugs for the three months periods before and after ADD was initiated retrospectively collected from the Swedish Prescribed Drug Register.	The number of drugs in use was estimated. Prescribing quality: 1. use of ≥10 drugs 2. use of ≥3 psychotropic drugs 3. use of long-acting benzodiazepines 4. drug-drug interactions (category D) 5. use of anticholinergic drugs 6. antipsychotics	The number of drugs in use was statistically lower before initiation of ADD (5.76 95%CI 5.71;5.80 vs. 7.15 95%CI 7.10;7.19). Proportion of patients using potentially harmful drug treatments was higher after initiation of ADD, only use of long-acting benzodiazepines and number of drug-drug interactions prevailed on the same or a bit lower level (not statistically tested).
Descriptive cross-sectional studies on ADD process or on patients' drug use (6)				
Mertens et al.,[120] 2019, the Netherlands Self-evaluation of the ADD process (cross-sectional study)	To evaluate the ADD process in community pharmacies, particularly making changes in medication dispensed via ADD	Participants: all ADD users from 8 community pharmacies (selected voluntary basis), mean number of the ADD users per pharmacy was 273 (±138). Data collection: a survey instrument was used to record changes made in medications dispensed via ADD during a three-week period in 2015.	Type of medication changes made (start, stop, dosage adjustment, other), drugs involved, procedure to effectuate the medication change, perceived necessity of the immediacy of each ADD adjustment, and time taken by pharmacy staff to effectuate the medication change.	261 ADD adjustments for 250 patients were made. Total number of changes was 365 (addition of a new drug n=127, dosage change n=124, drug discontinuation n=95). 135 of the 261 ADD adjustments (52%) were effectuated immediately, pharmacist considered that 36 of these could have been deferred until the next ADD order. Immediate adjustment was more time consuming than a deferred adjustment (p<0.001).

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Mertens et al.,[124] 2018, the Netherlands Controlled cross-sectional study	To compare characteristics and potential medication management problems of home-dwelling older adults with polypharmacy (≥5 drugs) using ADD and not using ADD	Study group: 188 randomly selected ADD users from 44 community pharmacies. Control group: 230 randomly selected non-ADD users from 44 community pharmacies. Inclusion criteria: >65 years, home dwelling, and using ≥5 drugs. Data collection: structured patient interviews performed by 44 community pharmacists using a medication management assessment tool. Cognitive function and frailty were also assessed with separate tools.	The medication management tool included 22 potential medication management problems, covering 4 domains: 1. functional, 2. organizational, 3. medication adherence, and 4. medication knowledge.	ADD users were older (median 80.5 years vs. 76 years, $p<0.001$), more commonly female (67% vs. 53%, $p<0.003$), and using more drugs (median 8 IQR 7-11 vs. 7 IQR 6-9, $p<0.001$) than non-ADD users. ADD users were more commonly cognitive impaired (42% vs. 20%, $p<0.001$) and were assessed frail (63% vs. 27%, $p<0.001$) than non-ADD users. ADD users had more potential medication management problems (median 8 IQR 5-10 vs. 3 IQR 2-5, $p<0.001$) than non-ADD users.
Belfrage et al.,[113] 2014, Sweden Controlled cross-sectional study using retrospective patient data	To compare the prevalence of suboptimal drug treatment in older hip fracture patients - with and without ADD	Study group: a randomized sample of 100 ADD patients (≥65 years) with hip fracture. Control group: a randomized sample of 100 non-ADD patients (≥65 years) with hip fracture. Data collection: two specialist physicians independently assessed the quality of drug treatment using STOPP/START tool.[87]	Suboptimal drug treatment: ≥1 STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) or ≥1 START (Screening Tool Alert to Right Treatment) outcome regarded as clinically relevant.	The mean number of inappropriate / missing drugs per person was higher among ADD users (1.92 vs. 1.06, $p<0.0001$), the prevalence of suboptimal drug use was more common among ADD users (86% vs. 55%, $p<0.0001$). After adjustment for age, sex, number of drugs, cognition and residence the risk of suboptimal drug treatment was higher among ADD users (OR 8.0; 95% CI 2.4; 26.9).

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Cheung et al.,[123] 2014, the Netherlands Retrospective cross-sectional study	To describe the nature and consequences of medication errors related to ADD	Data collection: medication errors related to ADD reported in a nationwide medication error reporting system by community pharmacies or hospitals during a 14-month period in 2012-2013.	The following aspects were quantitatively analysed from the incident reports: 1. person discovering incident 2. phase of medication process 3. immediate causes 4. nature of incident, healthcare provider's perspective 5. nature of incident, patient's perspective 6. harm to the patient.	Of the 15 111 reported incidents 268 (1.8%) related to ADD (community pharmacy n=227, hospital pharmacy n=41). Most commonly incidents reported from community pharmacies occurred in entering the prescription into the pharmacy information system (n=99) and filling the ADD pouch (n=43). The most common causes of the incidents were change in the patient's medicine regimen (n=55) or relocation (n=10).
Hammar et al.,[115] 2014, Sweden Retrospective cross-sectional study	To analyse potential drug-related problems (DRPs) in patients with ADD identified by an electronic expert support system used in Sweden	Participants: all patients who had drugs dispensed via ADD during a three month period in Sweden in 2013 (n=180 059). Data collection: prescribed drugs were collected from the national prescription repository. DRPs were detected by an electronic expert support used in Sweden.	7 indicators for potential DRPs: 1. therapy duplication 2. drug-drug interactions 3. high dose 4. geriatric warning 5. drug disease inferred 6. gender warning 7. paediatric warning	Mean age of the patients was 75.8 years (±17.5, range 1-110), mean number of drugs was 10 (±4.7, range 1-53). Potential DRPs were found in 76% of the patients, mean 2.2 DPRs per patient (±2.4, range 0-27). Older patients received a lower number of alerts than younger patients (not statistically tested). Most common alerts: drug-drug interaction (37% of the alerts), duplicate therapy (30%) and geriatric warning for high dose or inappropriate drugs (23%).

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Kwint et al.,[121] 2013, the Netherlands Controlled cross-sectional study	To investigate self-reported medication adherence and knowledge	Study group: a random sample of ADD patients (n=119) from 8 community pharmacies. Control group: a random sample of non-ADD patients (n=96) matched on age and gender. Inclusion criteria: ≥65 years of age, using ≥5 drugs, living at home or residential care home. Data collection: data was collected by interviewing patients.	Self-reported medication adherence was measured by Medication Adherence Report Scale (MARS). Medication knowledge was measured by asking the patients for the indications from their drugs.	Medication adherence to all drugs was higher among ADD users (ADD 91% vs. non-ADD 58%, $p<0.001$). Adequate medication knowledge was lower among ADD users (ADD 40% vs. non-ADD 79%, $p<0.001$).
Descriptive studies on perceptions and experiences (n=4)				
Mertens et al.,[122] 2018, the Netherlands Interview (cross-sectional)	To investigate patients' experiences on initiation and use of ADD	Participants: a sample of 62 ADD users from three pharmacies in the Netherlands. Data collection: patients were interviewed using a structured interview protocol.	Patients' experiences of ADD initiation, and advantages and disadvantages of ADD	Patients' median age was 79.5 years. The ADD initiation was discussed with 76% of the patients prior starting the service. 90% of patients expressed that ADD supported them with medication management. Perceived advantages (n=110): improved medication adherence and medication safety (59%) and patient's convenience (40%). Perceived disadvantages (n=37): problems with opening packages or pouches (41%) and can not read the printed text on the pouches (22%).

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Bardage et al.,[118] 2016, Sweden Cross-sectional survey	To assess preferences and experiences of ADD users	Participants and data collection: questionnaires were distributed through pharmacies to 4566 ADD users in 40 randomly selected municipalities in Sweden. Inclusion criteria: independent medicine users who can self-manage their medicines without assistance from primary care.	The survey included questions and statements about ADD regarding medication adherence and patient safety.	Response rate was 33% (n=1465), 64% of respondents were ≥65 years old. ADD was reported to help patients to correct dosing (93%), to identify the medicine (46%), and allows them to become more involved in decisions about their treatment (49%). 90% perceived it confusing to take part of the medicines ADD dispensed and part dispensed in packages. 37% perceived that generic substitution made it difficult to identify drugs. 40% called better information on the purpose and goal of their treatment, 25% called better information on changes in their drug regimens. A picture or description of the tablets were asked.
Bardage et al.,[35] 2014, Sweden Cross-sectional survey	To investigate healthcare professionals' perceived experience of ADD and its effects on patients' medication adherence and patient safety	Participants and data collection: questionnaires were sent via email to 915 physicians, 515 nurses, and 4118 assistant nurses who prescribe or administer ADD drugs to patients in 40 randomly selected municipalities in Sweden.	The surveys included questions and statements about ADD regarding medication adherence and patient safety.	Response rates were 31% (physicians), 43% (nurses), and 23% (assistant nurses). Healthcare professionals perceived that ADD reduces medication duplicates (63, 87, 81%), helps patients take their medications at the right time (69, 94, 84%), and reduces confusion among patients (70, 88, 74%). Physicians reported that prescribing procedure in ADD is complicated and poses a risk for patient safety. Physicians and nurses requested more information and training on ADD.

Reference, country, and study design/method	*Aim of the study*	*Study participants and data collection*	*Outcome measures*	*Main results*
Wekre et al.,[130] 2012, Norway Implementation study of the ADD service (survey)	To investigate 1. GPs' attitudes and experiences on introduction of ADD, and 2. GP's prescribing, communication, and collaborative work routines before and after the introduction of ADD	Study group: all GPs in Trondheim 2005: n=123; 2008: n=137. Control group: all GPs in Tromsø 2005: n=53; 2008: n=53. Data collection: the surveys were performed in 2005 (ADD not implemented in Trondheim or Tromsø) and 2008 (ADD implemented in Trondheim, not in Tromsø).	The survey instrument included questions on prescription routines and communication and cooperation with home care services and pharmacies.	Response rates were in Trondheim: 2005 67% and 2008 66%; and in Tromsø: 2005 75% and 2008 56%. The GPs in a study group had a positive attitude to ADD both before and after the implementation of the service. The majority of GP's (69%) wanted ADD to be continued. The GPs' prescription- and communication routines were improved only for the ADD users. The workload for GP was increased after implementation of ADD (p<0.001).

ADD=automated dose dispensing, CI=confidence interval, DRP=drug-related problem, GP=general practitioner, IQR=interquartile range, OR=odds ratio, PIM=potentially inappropriate medication, TTR= Time in Therapeutic Range

2.4.2 SUMMARY OF THE EVIDENCE ON OUTCOMES OF THE AUTOMATED DOSE DISPENSING

Summary of the outcomes and implications for studies is presented in Table 5. The ADD service may have positive outcomes on medication adherence.[121,129] The studies which explored the appropriateness of medication use imply that patients using the ADD service have more potentially inappropriate drugs or potentially harmful drug treatments in their drug regimens compared to patients not using ADD.[113-116] The studies also imply that number of drugs used might increase after the ADD service is initiated.[114,116]

Table 5. Summary of positive and negative outcomes or implications of ADD found in the studies included in the literature review covering the period from April 2012 to December 2019 (n=13). Positive outcome or implication is marked with a plus (+) and negative outcome or implication with a minus (-). The categories (appropriate drug use, medication safety and medication adherence) are derived from the aims of the studies included.

Study	*Appropriate drug use*	*Medication safety*	*Medication adherence*
Controlled cohort study (n=1)			
van Rein et al. 2017[129]			+
Uncontrolled cohort studies (n=2)			
Bobrova et al. 2019[114]	-		
Wallerstedt et al 2014[116]	-		
Descriptive cross-sectional studies on ADD process or on patients' drug use (n=6)			
Mertens et al. 2019[120]	*na*	*na*	*na*
Mertens et al. 2018[124]	*na*	*na*	*na*
Belfrage et al. 2014[113]	-		
Cheung et al. 2014[123]	*na*	*na*	*na*
Hammar et al. 2014[115]	-		
Kwint et al. 2013[121]			+
Descriptive studies on perceptions and experiences (n=4)			
Mertens et al. 2018[122]		+	-
Bargade et al. 2016[118]		+/-	
Bargade et al. 2014[35]		+/-	
Wekre et al. 2012[130]		+	

ADD= automated dose dispensing, na=not applicable

The evidence on the effectiveness of the ADD service is still scarce and vague; studies using rigorous study designs such as randomized control trials are still

missing. Economic evaluations were not considered nor were costs studied in any of the studies.

2.5 SUMMARY OF KEY FINDINGS OF THE LITERATURE

- Medication-related risks are common among older adults. Polypharmacy increases the risk of inappropriate drug use as well as drug-drug interactions. Other risks include excessive use of anticholinergic, psychotropic, sedative or serotonergic drugs which may induce adverse drug reactions and other drug-related problems.

- Different risk management tools have been developed to manage drug-related risks in older adults. The Beers criteria and Med75+ database are examples of different types of criteria used to identify potentially inappropriate drugs (PIMs). Also, medication reconciliation and collaborative medication reviews may prevent medication-related problems among older adults.

- The ADD service has been presented as a systemic defence to prevent medication risks in older adults using multiple medications. The ADD service is primarily used in the Nordic countries and in the Netherlands.

- The ADD was launched in Finland in 2002. The Ministry of Social Affairs and Health has published guidelines on good ADD practices. The Finnish Medicines Agency has published further regulations on ADD. There are more than 50 000 patients using the ADD service in Finland, most of them are clients of home care services or residents of nursing homes.

- The most recent studies on ADD imply that ADD may have positive outcomes on patients' medication adherence. Further evidence was found regarding the fact that patients using ADD have more potentially inappropriate drugs in their drug regimens than patients using standard dispensing procedures. In addition, implications that number of drugs used might increase after the ADD service was initiated were found.

3 AIMS OF THE STUDY

The study aimed to investigate existing evidence on outcomes of the ADD service, service's initiation process and evaluate service's impact on patients' drug use and quality of drug regimens. The specific aims of this study were:

- To systematically review the evidence for the influence of ADD on the appropriateness of medication use, medication safety, and costs in primary care.

- To investigate how the medication list was reconciled, what type of medication review was conducted, and what changes were made to medications when the ADD service is initiated for an individual patient in primary care in Finland.

- To investigate the impact of the ADD service with medication review on medication use and quality in older primary care patients in Finland.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

This doctoral thesis consists of four studies exploring the initiation process of the ADD service and outcomes of the service (Figure 6). Data were collected from various sources with various methods.

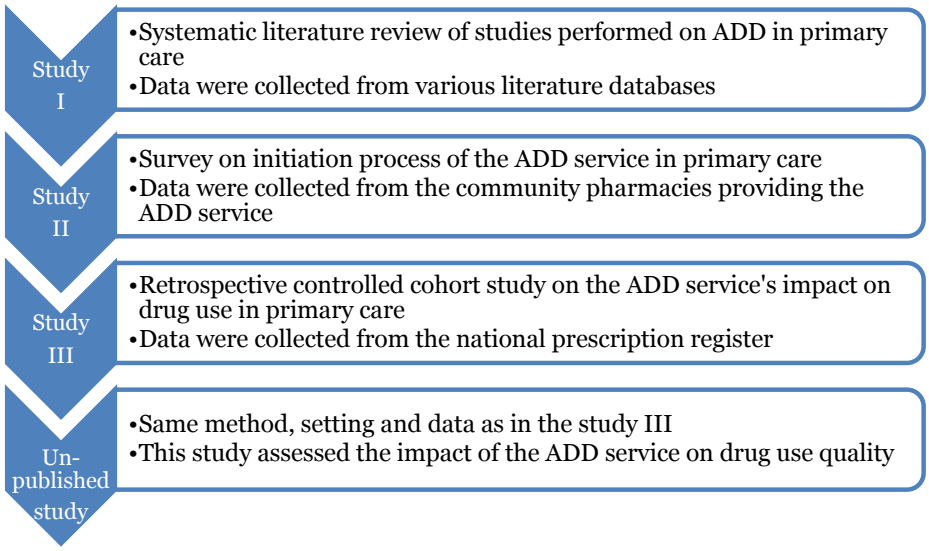

Figure 6. Study outline.

4.2 PREVIOUS STUDIES ON AUTOMATED DOSE DISPENSING – SYSTEMATIC LITERATURE REVIEW (I)

A literature search of the Study I was performed in April 2012 on the following databases: Medline, Medline in-process, and other non-indexed citations, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cinahl, Journals@Ovid, NHS Economic Evaluation Database (EED), Health Technology Assessment database (HTA), Database of Abstracts of Reviews of Effectiveness (DARE), and Embase. Key search terms included: automated medication/drug dispensing, automated medication/drug distribution, automated dose dispensing/distribution, automated dispensing system, multidose drug dispensing/distribution, and unit-dose dispensing/ distribution. An example of the search strategy is in Appendix 1. Reports and studies published from early 1995 to April 2012 were

included in the literature search. The reference lists of the studies selected were manually searched.

A study was included in the review if it was conducted in primary healthcare or nursing home settings, and the medicines were dispensed for patients in unit-dose pouches. The following PICO (Patients, Intervention, Comparison, Outcomes) was applied in this study: Patients (patients from primary healthcare or nursing homes), Intervention (ADD), Comparison (usual care/not ADD; not required), and Outcomes (appropriateness of medication use, medication safety, and costs). Qualitative studies and case reports were excluded.

Studies were selected independently by two reviewers, based on abstracts according to inclusion and exclusion criteria. Disagreements were resolved through discussion and consensus.

4.3 ASSESSMENT OF INITIATION PROCESS OF THE AUTOMATED DOSE DISPENSING SERVICE (II)

4.3.1 STUDY SETTING AND DATA COLLECTION

Espoonlahti Pharmacy was the larger of the two suppliers at the time of the study (267 vs. 60 client pharmacies). Therefore, the pharmacies purchasing unit-dose pouches from Espoonlahti Pharmacy were chosen as the target pharmacies. All new ADD users in these pharmacies during a 3-week (weeks 37, 38 and 39) period in autumn 2010 were included. All patients enrolled in the ADD service during the study period were eligible for the study.

A data collection sheet covering the ADD start-up process and changes made to the patient's medication during this process was developed and piloted in a small-scale study conducted in a single pharmacy in 2009. [131] Based on this pilot study, minor changes were made to the sheet. Two pharmacists further piloted the revised sheet in two pharmacies. The sheet was still slightly modified after this second pilot, according to the pharmacists' comments.

The sheet consisted of structured and open-ended questions. The structured questions included an open field for additional notes. The pharmacists were asked to record characteristics of the community pharmacy and the ADD user (location of the pharmacy, number of prescriptions dispensed per year, age and gender of the ADD user). The respondents were asked to record the patient's complete medication (prescription and over-the-counter medicines) before and after the ADD start-up and to categorize the changes made to the

patient's medication. Three types of medication reviews available in Finland were described in the data collection sheet.[102,132]

The data collection sheets were sent to all Espoonlahti Pharmacy customer pharmacies (n=267) with the unit-dose pouches they had ordered three weeks before the study period. A stamped and addressed return envelope, cover letter, and instructions for filling in the data collection sheet were sent with the sheets to the target pharmacies. The respondents had a choice of answering either on paper or via the Internet. The material was addressed to the pharmacist who was responsible for the ADD service. Two reminders were sent, the first to all target pharmacies along with the unit-dose pouches they had ordered from the dose dispensing unit and the second after the study period only to those pharmacies that enrolled new ADD users during the study.

4.3.2 DATA ANALYSIS AND STATISTICAL ANALYSIS

The responses were analysed anonymously. The structured quantitative data were entered into Excel for Mac 2008. Responses to questions concerning the organizations and the personnel involved in the medication review were combined in the analysis (Table 9). Four types of organizations were recognized, and the following categories were applied to 'community pharmacy', 'healthcare', 'dose dispensing unit', and 'care unit'.

Changes in patients' medications were categorized as technical or treatment-related changes, and further subcategories were developed under these main categories (Table 10). The technical changes were related to changes required in order to make the medication suitable for ADD. The treatment-related changes were related to patient care, e.g., a change was made to avoid an interaction.

Pearson's Chi-squared test was used to compare associations of the preparations' proportions used regularly, as needed and as a course before and after the initiation of the ADD service initiation process. *P* values less than 0.05 were considered statistically significant. The statistical tests were performed with PASW Statistics (release 18.0.3).

4.4 EVALUATION OF THE EFFECTIVENESS OF THE AUTOMATED DOSE DISPENSING SERVICE (III AND UNPUBLISHED STUDY)

4.4.1 STUDY SETTING, PATIENTS AND DATA SOURCES

The controlled cohort study design was applied. All primary care patients who were ≥65 years and were enrolled in the ADD service in 2007 in Finland and used the service at least one year after the start-up date were included in the study group. The patients were extracted from the customer register of Espoonlahti Pharmacy. A control patient for each patient in the study group was selected from the population register of the Social Insurance Institution by the personnel of the institution in June 2011. The control patients were matched with the study patients by gender, age (at the end of the year), area of patient's residence (hospital district) and the number of prescription drugs reimbursed during the period August–November in 2006. The number of active substances defined the number of prescription drugs reimbursed according to the Anatomical Therapeutic Chemical (ATC) classification system's 5th level.[133] These matching criteria were selected because these issues commonly affect drug use, and confounding could be avoided by matching in a cohort study.[134] The start-up date of the ADD service was used as an index date for both the study and control patients.

The Finnish National Prescription Register, which contains information on all reimbursed prescriptions for outpatients, was used as a data source.[135] Data on all prescriptions reimbursed during the 1-year periods before and after initiation of the ADD service were extracted for each patient in the study and control groups. A unique personal identification (ID) number was used to link the data from the customer register of Espoonlahti Pharmacy with the prescription data. Patients who had no drug purchases in the register before the ADD service was initiated (n=34) were omitted since this might indicate, that they have been living in an institution and their drug use might have been quite different compared to patients living at home (Figure 7). Also, patients who had manually dose dispensed drug purchases before the ADD service was initiated (n=37) were omitted since we aimed to study drug use in automatic dose dispensing service. If a matched control patient was not found, the patient was removed from the study group (n=67). As the aim was to study the older adult population, patients younger than ≥65 years were excluded from the study and control groups.

The Special Reimbursement Entitlement Register, which is also maintained by the Social Insurance Institution, was used as a source on the data on chronic diseases for the study and control patients. [136]

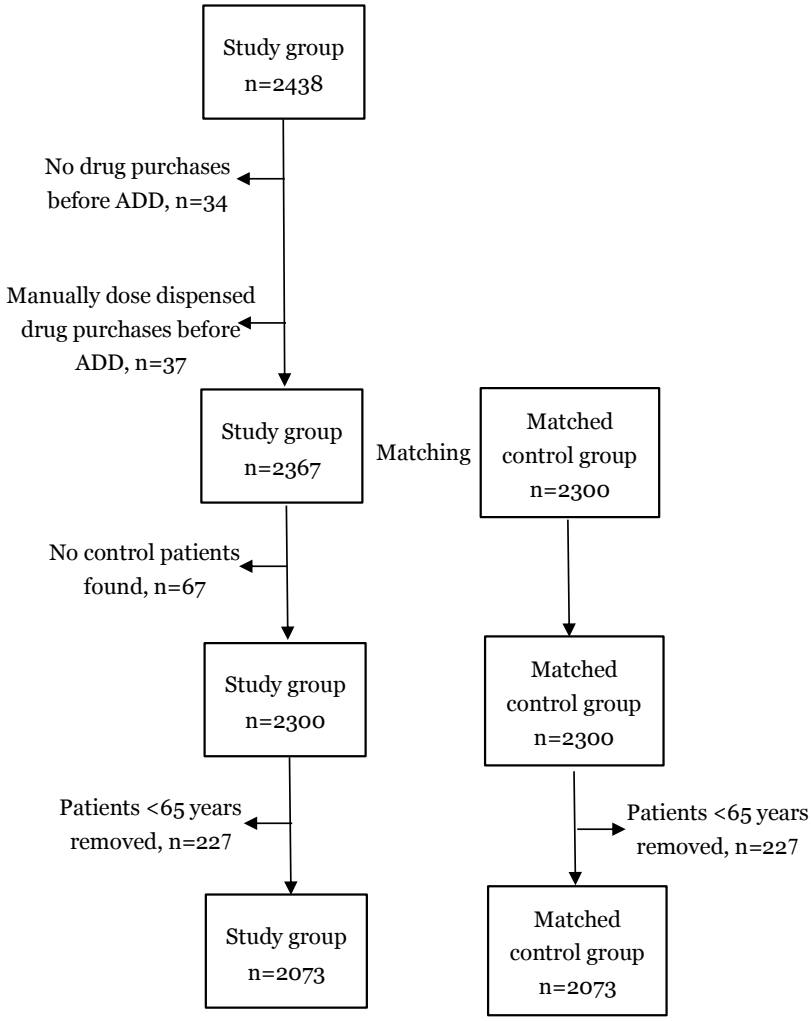

Figure 7. The selection process of the patients.

4.4.2 OUTCOME MEASURES AND DEFINITIONS

Study on drug use

In the Study III, drug use was calculated separately for each patient in the study and control groups during the 1-year periods before and after initiation of the ADD service. It was calculated as defined daily doses per day (DDD/day) by active substance derived from ATC 5th level.[133,137] For each patient, the first and last purchase dates of each drug (by ATC code) were identified and the number of days between these two time points was counted. The sum of the DDDs was counted from the first purchase date until the second last purchase date. The number of DDDs of the last purchase date was not counted in the sum since we could not predict the duration of drug use because the following purchase date was not known. To obtain DDD/day values, the sum of the DDDs was divided by the sum of the days.

A patient was assumed to be a new drug user if he/she had no purchases of a certain drug in the one year before ADD but there was at least one purchase in the one year after the ADD service was initiated. The drug use was assumed as discontinued if the patient had no purchases of a certain drug for one year after the ADD service was initiated but there was at least one purchase during the one year before ADD.

The 20 most used drugs (in DDDs) in the 2-year study period were chosen for the analysis. These 20 drugs covered 86% of all reimbursed drug use (in DDD) of the study group.

Study on the quality of drug regimens

The quality of patients' drug regimens was measured using two different criteria, the Beers criteria and the Swedish Indicators for Good Medication Use Among the Elderly.[53,85]

In this study, the update for the Beers criteria published in 2012 was applied.[85] Some of the medicines included in the criteria are either not marketed or not reimbursed in Finland, and thus, not suitable for this register study. Of all the medicines included in the Beers criteria, 21 medicines were suitable for this register study (Appendix 2). The proportions of the patients using at least one Beers drug during one year before and after the ADD service was initiated were calculated. A patient was assumed to be a Beers drug user if there was one purchase of the Beers drug during the study period.

Indicators for Good Medication Use Among the Elderly that was applied in this study was published in 2010 by The National Board of Health and Welfare, a government agency in Sweden.[53] Of these criteria, the criteria suitable for

this register study were chosen. These were anticholinergic drug use, long-acting benzodiazepine use, tramadol use, ≥3 psychotropic drug use, and ≥10 drug use. The lists of the long-acting benzodiazepines and anticholinergics were complemented by the lists published in Finland since there are differences between the medicines which are marketed in Finland and Sweden.[54]

The proportions were calculated of the long-acting benzodiazepine, tramadol, and anticholinergic drug users during one year before and one year after the ADD service was initiated. A patient was assumed to be a drug user if there was one purchase of specific drug during study periods. The proportions of the patients using ≥10 drugs and ≥3 psychotropic drugs were also calculated.

4.4.3 STATISTICAL ANALYSIS

Study on drug use

The difference in mean drug use in DDD/day was tested with the general linear model, using repeated measures analysis. The *p* values for group, time and time*group effects were calculated. The group effect compares the drug use of the study and control groups (not taking into account the initiation of the ADD service). The time effect compares the drug use before and after the initiation of the ADD service (not taking into account the study and control groups). The time*group takes both of these aspects into account.

The number of chronic diseases was used as a covariate in the analysis. After fitting the model, outliers in the values of the drug use were checked individually from the original register data. In 10 cases, the values of the drug use were removed from the data, due to an apparent error in the original register data. The differences between the proportions of the patients who started and discontinued the drug use in the study and control groups were tested with the Pearson's chi-squared test.

All tests were carried out with SPSS (version 18.0 for Mac, IBM SPSS, Armonk, NY). A difference was considered statistically significant if the *p*-value was less than 0.05.

Study on the quality of drug regimens

Logistic generalized linear mixed model (GLMM) was used to study the association between ADD initiation and drug use quality. The results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). The number of chronic diseases adjusted the odds ratios. Tests were performed with SAS using the Glimmix procedure. The group effect compares the drug use quality

of the study and control groups (not taking into account the initiation of the ADD service), the control group is a reference. The time effect compares the drug use quality before and after the initiation of the ADD service (not taking into account the study and control groups), the time before the ADD is a reference. The group*time takes both of these aspects into account. The control group is a reference and time is a constant (after the ADD initiation).

4.5 RESEARCH ETHICS

The University of Helsinki Viikki Campus Ethics Committee approved the study protocol (Studies II, III and unpublished study). The data of the studies did not contain any identifiable patient data (e.g., name, date of birth, city of residence or address). The data of the studies were collected before the general data protection regulation (GDPR) was applied in the European Union.

5 RESULTS

5.1 PREVIOUS STUDIES ON AUTOMATED DOSE DISPENSING – A SYSTEMATIC REVIEW COVERING EVIDENCE UNTIL 2012 (I)

Seven studies met the inclusion criteria (Figure 8). [17,47-50,138,139]

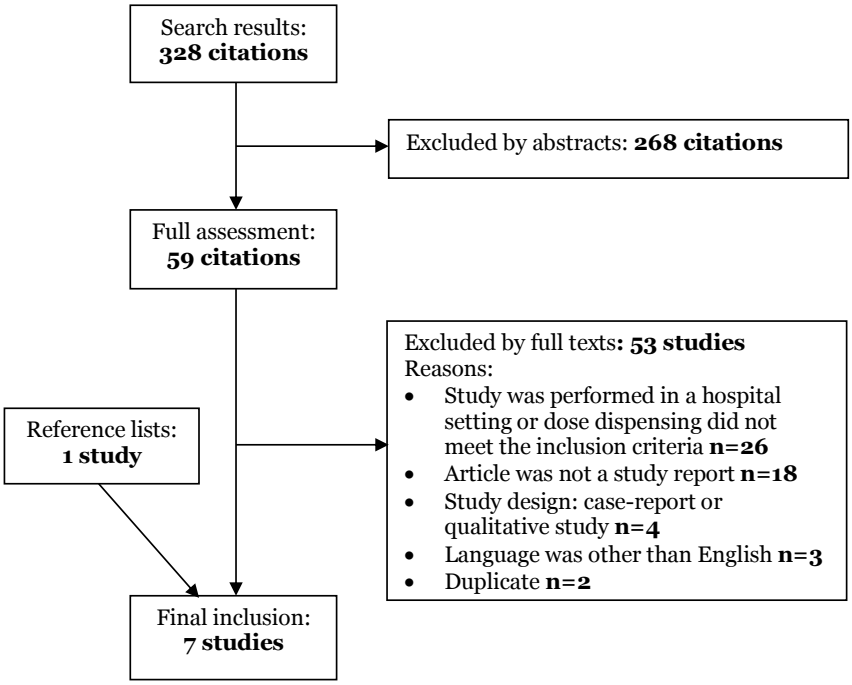

Figure 8. Flow chart of the study selection process.

The selected studies (n=7) are presented in Table 6. Six studies were conducted in the Nordic countries,[17,47-50,139] and one in the Netherlands.[138] Five studies were register-based.[17,47-50] Only one of the studies was a controlled cohort study.[50] One of the studies was an uncontrolled cohort study with a before-after design,[139] and the other studies were descriptive cross-sectional studies without any follow-up of the ADD intervention.[17,47-49,138] Randomized controlled studies were not found.

Table 6. Description and results of the studies on automated dose dispensing (ADD) in primary healthcare by 2012 (n=7).

Reference, country, and study design	*Aim of the study*	*Population and data collection*	*Outcome measures*	*Main results*
Controlled cohort study (n=1)				
Sjöberg et al.,[50] 2012, Sweden Controlled cohort study	To compare changes in drug treatments within and outside ADD	154 community-dwelling or nursing home residents ≥65 years of age (patients using ADD n=107, not using ADD n=47). Data on drug treatments were extracted from the medical records (t=0 months) and the Swedish Prescribed Drug Register (SPDR) (t=6 months). The multi-level analysis was performed, with drugs at the first level and individuals at the second.	The number of changed (withdrawn, dosage adjusted, or newly prescribed) and not changed drugs.	The risk of medication to be classified as unchanged was higher among ADD users (OR 1.66, 95% CI 1.20-2.31, adjusted for age, sex, cognition, year of data collection, the subgroup of the drug).
Uncontrolled cohort study (n=1)				
Wekre et al.,[139] 2010, Norway Cohort study	To study the impact of ADD on inconsistencies in medication records between GPs and home care services	A convenience sample of 59 patients. Medication records were collected six months before and one year after the ADD implementation.	Number of discrepancies between the patients' medication records at the GPs and the home care services	ADD did not change the number of medication records with discrepancies (before 47 and after 45 out of 59, p=0.774, n.s.), but reduced the total number of discrepancies by 34% (p<0.001).

Reference, country, and study design	*Aim of the study*	*Population and data collection*	*Outcome measures*	*Main results*
Descriptive cross-sectional studies on ADD process or on patients' drug use (n=5)				
Sjöberg et al.,[49] 2011, Sweden Controlled cross-sectional study	To investigate association between ADD and quality of drug treatment	All community-dwelling or nursing home residents from Västra Götaland ≥65 years of age in late 2007 and having ≥2 healthcare visits and ≥2 diagnosis in 2005-2007. Study group: ADD users (n=4927). Control group: patients not using ADD (n=19 219). Data were collected from the SPDR in 2007 and linked with register data on patient diagnoses and residence.	5 quality indicators for potential IDU: 1. use of ≥10 drugs 2. use of long-acting benzodiazepines 3. use of anticholinergic drugs 4. use of ≥3 psychotropic drugs 5. potential drug-drug interactions	ADD users had a higher prevalence of all indicators of potential IDU (5.9-55.1%) than the control population (2.6-4.9%) (p<0.0001). After adjustment for age, sex, burden of disease, and residence, risk of all indicators of potential IDU were higher among ADD users (ORs 1.36-5.48; 95% CI 1.18-6.30).
Olsson et al.,[48] 2010, Sweden Cross-sectional study	To study the extent and quality of drug prescribing in younger elderly (65-79 years) and older elderly (≥80 years) receiving ADD	All residents of nursing homes and dementia special care units ≥65 years of age (n=3705) from the County of Jönköping. Data on prescribed drugs were collected from the national pharmacy drug register.	5 quality indicators for potential IDU: 1. use of long-acting benzodiazepines 2. use of anticholinergic drugs 3. drug duplications 4. use of ≥3 psychotropic drugs 5. potential drug-drug interactions	Potential IDU prevalences ranged from 7.6% to 41.2%. Prevalences of potential IDU were mainly higher among younger (65-79 years) than older (≥80 years) residents (not statistically tested).

Reference, country, and study design	*Aim of the study*	*Population and data collection*	*Outcome measures*	*Main results*
van den Bemt et al.,[138] 2009, the Netherlands Cross-sectional study	To explore frequency of medication administration errors and potential risk factors for these errors in nursing homes using ADD	In all, 2025 administrations to 127 residents of 3 nursing homes were observed by one pharmacy technician.	Medication administration error rates	The administration error rate for all administered medications observed (via ADD and without ADD) was 21.2% (n=428 errors). Most common error type was wrong administration technique (n=312). The risk for administration errors was higher when medicine was not supplied by ADD (OR 2.92; 95% CI 2.04-4.18).
Johnell and Fastbom,[17] 2008, Sweden Controlled cross-sectional study	To investigate whether the use of ADD is associated with potential IDU	All Swedes ≥75 years of age who were registered in SPDR. Study group: ADD users (n=122 413). Control group: patients not using ADD (n=608 692). Data were collected from the SPDR in 2005.	4 quality indicators for potential IDU: 1. use of long-acting benzodiazepines 2. use of anticholinergic drugs 3. use of ≥3 psychotropic drugs 4. potential drug-drug interactions	ADD users had a higher prevalence of all indicators of potential IDU (8.8-22.1%) than the control population (2.4-4.9%). After adjustment for age and number of dispensed drugs, risk of using any IDU, anticholinergic drugs and ≥3 psychotropic drugs were higher among ADD users (ORs 1.43-4.93; 95% CI 1.40-5.17). Contrasting relationship prevailed for long-acting benzodiazepines among women and potentially serious drug-drug interactions among women and men (ORs 0.69-0.80; 95% CI 0.66-0.83).

Reference, country, and study design	*Aim of the study*	*Population and data collection*	*Outcome measures*	*Main results*
Bergman et al.,[47] 2007, Sweden Cross-sectional study	To investigate quality of drug therapy among nursing home residents using ADD	All nursing home residents ≥65 years of age (n=7904) from Gothenburg area. Data were collected from the Swedish national drug register for ADD users.	5 quality indicators for potential IDU: 1. use of long-acting benzodiazepines 2. use of anticholinergic drugs 3. drug duplications 4. use of ≥3 psychotropic drugs 5. potential drug-drug interactions	Potential IDU prevalences ranged from 12.1% to 45.2% among nursing home residents. The proportion of potential IDU was higher among 65-79 year-old residents than those ≥80 years old (p 0.001-0.015).

ADD=automated dose dispensing, DRP=drug-related problem, GP=general practitioner, IDU=inappropriate drug use, n.s.=not significant, SPDR=Swedish Prescribed Drug Register

Summary of outcomes and implications of the studies is presented in Table 7.

Table 7. Summary of positive and negative outcomes or implications of ADD found in the studies included in the literature review until April 2012 (n=7). Positive outcome or implication is marked with a plus (+) and negative outcome or implication with a minus (-). The categories (appropriate drug use and medication safety) are derived from the aims of the studies included.

Study	*Appropriate drug use*	*Medication safety*
Controlled cohort study (n=1)		
Sjöberg et al. 2012[50]	-	
Uncontrolled cohort study (n=1)		
Wekre et al. 2010[139]		+
Descriptive cross-sectional studies on ADD process or on patients' drug use (n=5)		
Sjöberg et al. 2011[49]	-	
Olsson et al. 2010[48]	-	
van den Bemt et al. 2009[138]		+
Johnell et al. 2008[17]	-	
Bergman et al. 2007[47]	-	

ADD= automated dose dispensing

Appropriate drug use

Five studies explored appropriateness of medication use (Table 6). [17,47-50] Potentially inappropriate drug use was investigated in four of the studies.[17,47-49] These four studies applied descriptive cross-sectional study design and were conducted in Sweden. The following quality indicators were used to measure inappropriate drug use: use of long-acting benzodiazepines, use of anticholinergic drugs, use of three or more psychotropic drugs, drug duplications, use of 10 or more drugs, and potential drug-drug interactions.[53]

The ADD users and non-ADD users quality of drug use was investigated in two descriptive cross-sectional studies.[17,49] Patients using the ADD service were those with a higher prevalence of potentially inappropriate drug use according to all quality indicators (ADD 5.9-55.1% vs. non-ADD 2.4-4.9%). The representative population-based register study reveil that the risk of using anticholinergic and three or more psychotropic drugs was higher among ADD users (ORs 1.43-4.93; 95% CI 1.40-5.17; adjusted for age and number of drugs dispensed), while the risk use of long-acting benzodiazepines among women and drug-drug interactions among women and men was lower among ADD users (ORs 0.69-0.80; 95% CI 0.66-0.83; adjusted for age and number of drugs dispensed).[17] The regional register study reveil that the risk for inappropriate drug use were higher among the ADD users according to all

indicators applied (ORs 1.36-5.48; 95% CI 1.18-6.30; adjusted for age, sex, the burden of disease, and residence).[49]

In the cross-sectional regional studies, it was found that the prevalence of potentially inappropriate drug use was higher among 65-79-year-old ADD users than at least 80 years old users.[47,48]

A controlled cohort study design was applied to study drug treatment changes in Sweden.[50] ADD users drug treatments' were more likely to remain unchanged when compared to patients using a standard dispensing procedure (OR 1.66, 95% CI 1.20-2.31, adjusted for age, sex, cognition, year of data collection, and the subgroup of the drug).

Medication safety

Two of the studies investigated the influence of ADD on medication safety (Table 6), of which one was an uncontrolled cohort study[139] and the other descriptive cross-sectional study.[138]

The uncontrolled cohort study conducted in Norway explored the impact of ADD on inconsistencies in medication records between general practitioners and home care services.[139] The implementation of ADD reduced discrepancies in medication records by 34% ($p<0.001$) between the general practitioners and home care services compared to situation six months before the ADD implementation.

The descriptive cross-sectional study investigated the frequency of medication administration errors and potential risk factors for these errors in nursing homes using ADD.[138] The risk of administration errors was higher when the medication was not supplied by ADD (OR 2.92; 95% CI 2.04-4.18).

Costs

Economic evaluation was not performed and costs were not studied in any of the studies.

5.2 INITIATION PROCESS OF THE AUTOMATED DOSE DISPENSING SERVICE (II)

During the study period, 325 patients in 110 community pharmacies were enrolled to the ADD service. The data collection sheet was filled for 147 patients resulting 45% as a response rate.

Among the study population, most of the patients were 75 years of age or older (77%), and 64% of them were women. Most commonly patients received help with their drug regimens from the personnel of the home care services (50% of the patients) or the nursing home/assisted living residence (41% of the patients).

5.2.1 MEDICATION RECONCILIATION

Most commonly two information sources were used in medication reconciliation (44%) (Table 8) and only one source was used in 37% of the cases. The existing medication list was a reliable source in medication reconciliation only in 14% of the cases. However, a medication list was used as a source in 71% of the cases. The personnel of home care services (39%) and nursing home/assisted living residences (33%) were other most often used sources in medication reconciliation.

Table 8. The number of sources used in medication reconciliation (n=147) before ADD was initiated, and the most common combinations of the sources.

Sources used in medication reconciliation	Proportion of patients	
	%	n
One source	37	54
Medication list[a]	14	20
Personnel of nursing home/assisted living residence	11	16
Personnel of home care services	10	14
Other sources	3	4
Two sources	44	65
Medication list[a] and personnel of home care services	20	29
Medication list[a] and personnel of nursing home/assisted living residence	15	22
Medication list[a] and family member, relative, or friend	2	3
Medication list[a] and health centre	2	3
Personnel of home care services and hospital	2	3
Other combinations	3	5
Three sources	15	22
Medication list[a], personnel of home care services, and health centre	7	11
Medication list[a], personnel of nursing home/assisted living residence, and health centre	5	7
Other combinations	3	4
Four sources	4	6
Medication list[a], personnel of nursing home/assisted living residence, health centre, and dispensing records of the pharmacy	2	3
Other combinations	2	3

[a] Medication list received from the patient or nursing staff did not necessarily include complete medication.

5.2.2 MEDICATION REVIEW

For the majority of the patients (96%) some type of medication review was conducted (Table 9). Most oftenly the prescription review was conducted (69% of all patients), which is the least comprehensive review.[132] Most often the dose dispensing unit (73%), a community pharmacy (66%), and healthcare (71%) were involved in the medication review process. In 63% of all cases, a physician was involved in the review process. The community pharmacist estimated that they spent on average 38 minutes (SD 31) per patient in reconciling the medication list and reviewing the medication.

Table 9. Type of medication review conducted for the patients and the number of organizations involved in a medication review (n=147).

Type of medication review	Portion of patients		Number of organizations involved in a medication review[d]							
			1		2		3		4	
	%	n	%	n	%	n	%	n	%	n
Prescription review[a]	69	101	10	15	26	38	26	38	7	10
Medication review[b]	12	17	2	3	3	4	5	8	1	2
Prescription and medication review	10	15	-	-	1	2	9	13	-	-
Comprehensive medication review[c]	3	5	1	2	1	1	-	-	1	2
Other types of review	2	3	-	-	1	1	1	2	-	-
No review	4	6	-	-	-	-	-	-	-	-

[a] Prescription review: A review by a healthcare professional (physician, nurse, pharmacist) checking the medicine dosage and administration times against the approved clinical practice, detecting eventual overlapping or incompatible medications.[132]
[b] Medication review: As part of routine patient examination and treatment-planning process, a review of medication, its need, and rationality, conducted by a physician.[132]
[c] Comprehensive medication review: A medication review procedure initiated by the attending physician and performed in collaboration with a specially trained pharmacist and other healthcare professionals. This review includes a comprehensive clinical review of all medications used to resolve drug-related problems and a case conference.[102,132]
[d] Following organizations were recognized: community pharmacy, healthcare, dose-dispensing unit, and care unit.

5.2.3 CHANGES TO MEDICATION

The mean number of medicines used per patient was 10.3 (SD 3.8) (counted by the Anatomical Therapeutic Chemical classification 5th level codes) before the ADD service was started and medication review conducted.[133] The mean number was the same (mean 10.3, SD 3.8) after initiation of the ADD service. Before the ADD service was initiated, 80.6% of all drugs were used regularly, 18.1% as needed and 1.3% as a course (e.g., antibiotics). After initiation, the proportions were respectively 81.3, 17.9 and 0.8%. Changes in these proportions were not statistically significant (*p* values, respectively 0.644, 0.878, 0.307). A total of 68% of all drugs used by the patients were dispensed via ADD.

In total, 593 changes were made to patients' medication regimens (Table 10). The mean number of changes per patient was 4.0 (range 0-14, SD 2.5). Starting the ADD service did not result any change for the mean number of medicines. However, changes to medications were made for 97% of the patients. Most of the changes were made due to technical reasons (78% of all changes). Generic

substitution (57% of all changes) was the most common reason. A fifth of the changes (22%) were made due to treatment-related reasons. Treatment-related changes were made for 43% of the patients, while technical changes were made for 93% of the patients. Sixty one per cent of the treatment-related changes were made for patients using more than ten medicines before ADD was initiated. Most commonly the treatment-related changes were made in medicines used for nervous, alimentary tract and metabolic or cardiovascular system diseases (proportions respectively 41, 26, 17% of the treatment-related changes).

Table 10. Reasons for changes (n=593) in patients' (n=147) medications.

Reason	Proportion of changes	
	%	n
I Technical reasons	*78*	*460*
Generic substitution	57	336
Medication was added: halving a tablet is avoided in ADD	11	70
Medication was discontinued: halving a tablet is avoided in ADD	8	49
Other reasons	1	5
II Treatment-related reasons	*22*	*133*
Medication was discontinued	7	44
Medication was added	4	26
Dose was decreased	4	21
Medication was changed to be used as needed	2	11
Dose was increased	2	10
To avoid an interaction (medication was discontinued or time of administration was changed)	2	10
Medication was changed to be used regularly	1	5
Other reasons	1	6

ADD: automated dose dispensing

5.3 AUTOMATED DOSE DISPENSING SERVICE'S IMPACT ON MEDICATION USE AND QUALITY (III AND UNPUBLISHED STUDY)

There were 2073 patients in the study and control groups (Figure 7). Most of the patients in both groups were female (73%) and >75 years of age (85%). The mean number of used reimbursed prescription drugs was 6.5 (SD 3.5; counted during the four months period before the study period).

There were differences between the study and control groups in terms of chronic diseases (Table 11). Patients in the study group more often suffered from Alzheimer's disease, diabetes, severe psychotic or other severe mental

disorders, Parkinson's disease and epilepsy than patients in the control group. The proportion of patients suffering from dyslipidemia, glaucoma and chronic asthma or other chronic obstructive pulmonary diseases were higher in the control group than in the study group.

Table 11. Prevalence of diagnosed chronic diseases in the study (n=2073) and control (n=2073) groups.

Diagnosed disease (in late 2006)	Study % (n)	Control % (n)
Chronic heart or cardiovascular disease	59.9 (1242)	62.4 (1293)
Alzheimer's disease	24.4 (506)	6.5 (134)
Diabetes mellitus	19.2 (399)	16.6 (344)
Dyslipidemia	10.0 (207)	12.7 (263)
Severe psychosis and other severe mental disorders	9.4 (195)	2.4 (50)
Glaucoma	9.2 (190)	12.5 (260)
Chronic asthma or other chronic obstructive pulmonary diseases	9.2 (190)	11.9 (247)
Thyroid insufficiency	6.4 (132)	6.8 (141)
Disseminated connective tissue diseases, rheumatoid arthritis, and comparable conditions	5.6 (117)	5.0 (103)
Parkinson's disease	4.0 (82)	1.6 (33)
Epilepsy	3.0 (62)	1.3 (27)
Cancer	3.0 (62)	3.9 (81)
Other diseases	7.2 (149)	6.8 (140)

5.3.1 DRUG USE

The drug use was reduced in 11 of the 20 most-used active substances studied (p values from <0.001 to 0.041; the time and group effects were taken into account in the analysis, and the drug use was adjusted by the number of chronic diseases) (Table 12). The reduction was observed in the following substances: hypnotics (temazepam and zopiclone), drugs for cardiovascular diseases (simvastatin, ramipril, amlodipine, isosorbide mononitrate, bisoprolol and metoprolol), donepezil (used for Alzheimer's disease), paracetamol (used for pain) and metformin (used for diabetes).

During the follow-up period, there were more starts and discontinuations in the study group than in the control group (Table 13). The zopiclone, temazepam and calcium combinations were more actively started and discontinued in the study group. Glimepiride and metoprolol were more actively started, while isosorbide mononitrate was more actively discontinued in the study group.

Table 12. Drug use (DDD/day) adjusted by the number of chronic diseases in the study and control groups before and after the automated dose dispensing (ADD) service was initiated. The 20 most-used (in DDDs) drugs among the study group were chosen for the analysis.

Active substance (ATC code)	Study group (n=2073)		Control group (n=2073)		*p* values		
	Before ADD Mean	After ADD Mean	Before ADD Mean	After ADD Mean	Group effect	Time effect	Time*group effect
Cardiovascular system							
Furosemide (C03CA01)	1.69	1.67	1.45	1.57	0.121	0.488	0.060
Ramipril (C09AA05)	2.21	2.04	2.42	2.58	**0.003**	0.922	**0.033**
Enalapril (C09AA02)	1.32	1.22	1.53	1.50	**0.005**	0.528	0.188
Bisoprolol (C07AB07)	0.53	0.42	0.57	0.56	**<0.001**	**0.002**	**<0.001**
Metoprolol (C07AB02)	0.55	0.48	0.57	0.57	**0.035**	0.386	**<0.001**
Amlodipine (C08CA01)	1.40	1.16	1.27	1.32	0.782	**0.010**	**<0.001**
Isosorbide mononitrate (C01DA14)	0.81	0.67	0.79	0.79	0.057	0.186	**<0.001**
Simvastatin (C10AA01)	1.27	1.14	1.20	1.28	0.511	0.097	**<0.001**
Nervous system							
Zopiclone (N05CF01)	1.01	0.95	0.97	0.99	0.981	0.382	**0.014**
Temazepam (N05CD07)	1.02	0.82	1.04	1.03	**0.015**	**0.032**	**<0.001**
Citalopram (N06AB04)	0.88	0.86	0.89	0.90	0.623	0.449	0.624
Mirtazapine (N06AX11)	0.85	0.76	0.71	0.73	0.068	0.411	0.060
Donepezil (N06DA02)	1.15	1.11	1.12	1.21	0.475	**0.045**	**0.021**
Memantine (N06DX01)	0.87	0.87	0.87	0.91	0.327	0.072	0.307
Paracetamol (N02BE01)	0.43	0.42	0.37	0.41	**0.032**	0.528	**0.041**
Alimentary tract and metabolism							
Lactulose (A06AD11)	2.22	2.10	1.76	1.76	**0.044**	0.072	0.593
Glimepiride (A10BB12)	1.46	1.37	1.62	1.63	**0.033**	0.366	0.158
Metformin (A10BA02)	0.85	0.81	0.81	0.84	0.861	0.855	**0.002**
Calcium combinations (A12AX)	0.94	0.82	0.88	0.83	0.697	0.151	0.545
Pantoprazole (A02BC02)	0.76	0.67	0.67	0.65	0.064	**0.012**	0.059

ATC: anatomical therapeutic chemical classification system; ADD: automated dose dispensing; DDD: defined daily dose.

Table 13. Proportions of patients who started and discontinued drug use in the study and control groups. The 20 most-used (in defined daily doses) drugs among the study group were chosen for the analysis.

Active substance (ATC-code)	Started drug use[a]			Discontinued drug use[b]		
	Study % (n)	Control % (n)	*p* value[c]	Study % (n)	Control % (n)	*p* value[c]
Cardiovascular system						
Furosemide (C03CA01)	17.7 (160)	18.8 (120)	0.581	5.1 (40)	8.9 (51)	**0.005**
Ramipril (C09AA05)	17.5 (48)	20.9 (48)	0.330	9.9 (25)	13.7 (29)	0.202
Enalapril (C09AA02)	9.9 (18)	13.9 (28)	0.225	11.4 (21)	13.9 (28)	0.447
Bisoprolol (C07AB07)	13.1 (85)	13.8 (95)	0.720	6.2 (37)	6.8 (43)	0.677
Metoprolol (C07AB02)	8.5 (35)	4.2 (14)	**0.017**	6.2 (25)	9.8 (35)	0.067
Amlodipine (C08CA01)	18.6 (49)	19.6 (55)	0.765	14.1 (35)	13.5 (35)	0.846
Isosorbide mononitrate (C01DA14)	11.9 (48)	10.1 (45)	0.397	9.6 (38)	5.4 (23)	**0.021**
Simvastatin (C10AA01)	12.1 (56)	15.7 (88)	0.103	6.5 (28)	9.6 (50)	0.080
Nervous system						
Zopiclone (N05CF01)	22.1 (94)	14.9 (57)	**0.008**	25.6 (114)	18.1 (72)	**0.009**
Temazepam (N05CD07)	22.9 (73)	11.2 (25)	**<0.001**	23.6 (76)	13.1 (30)	**0.002**
Citalopram (N06AB04)	17.2 (59)	21.8 (29)	0.246	19.3 (68)	22.4 (30)	0.451
Mirtazapine (N06AX11)	24.6 (73)	31.4 (38)	0.152	15.2 (40)	25.2 (28)	**0.021**
Donepezil (N06DA02)	17.0 (39)	29.5 (18)	**0.029**	10.0 (21)	6.5 (3)	0.469
Memantine (N06DX01)	30.6 (75)	31.3 (21)	0.909	4.0 (7)	2.1 (1)	0.548
Paracetamol (N02BE01)	39.0 (316)	43.1 (169)	0.174	29.5 (207)	35.0 (120)	0.074
Alimentary tract and metabolism						
Lactulose (A06AD11)	40.6 (162)	40.2 (49)	0.931	28.4 (94)	38.1 (45)	**0.049**
Glimepiride (A10BB12)	13.1 (26)	6.1 (11)	**0.014**	19.2 (41)	13.8 (27)	0.143
Metformin (A10BA02)	10.0 (27)	14.0 (38)	0.159	12.6 (35)	9.7 (25)	0.274
Calcium combinations (A12AX)	59.8 (297)	38.6 (134)	**<0.001**	41.0 (139)	20.8 (56)	**<0.001**
Pantoprazole (A02BC02)	28.2 (104)	25.7 (67)	0.485	23.4 (81)	29.5 (81)	0.088

ATC: anatomical therapeutic chemical classification system. [a]Drug use was considered as started if the patient did not fill any prescriptions for one year before ADD but filled at least one prescription for 1year after ADD was initiated. [b]Drug use was considered discontinued if a patient did not fill any prescriptions for one year after ADD initiation but filled at least one prescription for one year before ADD was initiated. [c]Chi-squared test.

5.3.2 QUALITY OF DRUG REGIMENS

The risk of use of at least one potentially inappropriate drug according to the Beers criteria was lower in the study group after initiation of ADD when the results were adjusted by the number of diseases (OR 0.737; 95% CI 0.574-0.946) (Table 14). The proportion of the users of 10 or more drugs was, due to the matching, same in both groups (9.8%) before the ADD service was initiated. The risk of use of 10 or more drugs was higher in the study group after initiation of ADD (OR 2.151; 95% CI 1.762-2.626) when results were adjusted by the number of diseases. Also, the risk of use of at least three psychotropic drugs was higher in the study group after initiation of ADD (OR 3.979 95% CI 2.811-5.632). The risks of use of anticholinergic drugs, tramadol or long-acting benzodiazepines were not statistically significantly higher or lower in the study group after the initiation of ADD.

Table 14. The proportion of potentially inappropriate drug users according to the criteria applied in the study and control groups before and after the automated dose dispensing (ADD) service was initiated.

Criterion	Study group		Control group		Group[a]	Time[b]	Group*Time[c]
	Before ADD	After ADD	Before ADD	After ADD			
	% (n)	% (n)	% (n)	% (n)	OR (95% CI)	OR (95% CI)	OR (95% CI)
At least 1 Beers drug	8.9 (184)	7.1 (147)	11.2 (233)	9.4 (194)	**0.752 (0.623-0.908)**	**0.799 (0.687-0.930)**	**0.737 (0.574-0.946)**
Anticholinergic drugs	10.1 (210)	9.1 (188)	6.9 (144)	7.8 (162)	**1.331 (1.096-1.615)**	1.002 (0.858-1.172)	1.175 (0.917-1.505)
Long-acting benzodiazepines	3.3 (69)	2.2 (46)	3.6 (75)	3.2 (66)	0.794 (0.578-1.090)	**0.760 (0.590-0.979)**	0.689 (0.449-1.055)
Tramadol	3.4 (70)	3.1 (64)	2.9 (61)	3.1 (64)	1.069 (0.794-1.440)	0.979 (0.764-1.254)	0.996 (0.675-1.469)
≥3 psychotropic drugs (regularly or as-needed)	6.7 (139)	8.8 (182)	2.1 (44)	2.4 (49)	**3.633 (2.773-4.759)**	1.223 (0.966-1.548)	**3.979 (2.811-5.632)**
≥10 drugs (regularly or as-needed)	9.8 (204)	20.6 (428)	9.8 (203)	10.6 (219)	**1.410 (1.200-1.657)**	**1.668 (1.451-1.919)**	**2.151 (1.769-2.626)**

ADD: automated dose dispensing; OR: odds ratio; CI: confidence interval.

[a] Main effect, the control group is a reference, odds ratios are adjusted by the number of diseases.

[b] Main effect, before ADD is a reference, odds ratios are adjusted by the number of diseases.

[c] Interaction term, the control group is a reference and time is a constant (after the ADD), odds ratios are adjusted by the number of diseases.

5.4 SUMMARY OF THE RESULTS

Study I: Previous studies on ADD until 2012
The findings suggest that patients using the ADD service were those having more inappropriate drug use than the patients using the standard dispensing procedure. At the same time, ADD may pose a risk of continuing the drug treatment unchanged. The findings also suggest that the ADD service may improve medication safety in terms of reducing discrepancies in the documentation of patient medication records in primary healthcare.
Literature review of this thesis: Previous studies on ADD from 2012 until 2019
The studies imply that ADD may have positive outcomes on patients' medication adherence. Further evidence was found on the fact that patients using the ADD service have more potentially inappropriate drugs in their drug regimens than patients using the standard dispensing procedure. In addition, implications that the number of drugs used might increase after initiation of the ADD service were found.
Study II: Evaluation of the ADD service's initiation process
The medication list was incomplete for more than half of the patients. Some type of medication review, most commonly a prescription review, was conducted for most of the patients. Most of the changes were technical, but also treatment-related changes were made during the initiation process. On average, community pharmacists spent a bit more than half an hour in reconciling the medication list and reviewing the medication for one patient. Results imply that the medications are not always appropriate before the patients are enrolled in the ADD service. On the other hand, results suggest that medication review is short and simple.
Study III: Evaluation of the ADD service's impact on medication use
The findings suggest that ADD decreased drug use in a one-year observation period. The decrease was found in eleven of the top 20 active substances used. ADD service patients also had more starts and discontinuations in their drug use than matched control patients.

Unpublished study: Evaluation of the ADD service's impact on the quality of drug regimens
The quality of drug regimens may be improved after the initiation of the ADD service when explicit inappropriate drug use criteria measured the quality of drug use. The risk of inappropriate drug use was lower after the initiation of the ADD service when quality was measured with the Beers criteria. However, when the quality of drug use was measured with more complex criteria, the quality may not be improved. The risks of use of ten or more drugs and three or more psychotropic drugs were higher after initiation of the ADD service.

6 DISCUSSION

6.1 PREVIOUS STUDIES ON AUTOMATED DOSE DISPENSING (I)

The literature review until 2012 reveals that only a few studies had investigated the outcomes of the ADD service in primary care, and the scientific evidence is too limited to draw any explicit conclusions on its effectiveness in improving the quality of pharmacotherapy.[17,47-50,138,139] The findings of the studies reviewed suggest that patients using the ADD service were those having more inappropriate drug use than the patients using the standard dispensing procedure.[17,47-49] At the same time, ADD may pose a risk of continuing the drug treatment unchanged for an unnecessarily long period if the medication is not regularly reviewed.[50] The findings also suggest that the ADD service may have positive outcomes on medication safety in terms of reducing discrepancies in the documentation of patient medication records in primary healthcare.[139]

The studies on ADD until end of the year 2019 were reviewed as a part of this thesis literature review (chapter 2.4). The review reveals that since the first systematic literature review was conducted, still only a limited number of studies on ADD have been published.[35,113-116,118,120-124,129,130] In addition, the quality of study designs and research methods had weaknesses, and thus, robust conclusions on outcomes of the ADD service can not be drawn.

In these more recent studies, further evidence was found of the fact that patients using the ADD service have more potentially inappropriate drugs or potentially harmful drug treatments in their drug regimens than the patients using the standard dispensing procedure.[113-116] Implications that number of used drugs might increase after initiation of the ADD service were found.[114,116] On the other hand, ADD may have positive outcomes on patients' medication adherence.[121,129] Further evidence of positive impact on patients' medication adherence was found in a recent randomized control trial.[140]

The studies indicated that patients using the ADD scheme include those with more complicated drug regimens and high-risk medications, such as anticholinergics and psychotropics.[17,49,113,116] In Study III, it was found that the prevalence of severe central nervous system diseases (e.g., Alzheimer disease and Parkinson's disease) is high among patients using ADD. These diseases may lead to complicated drug combinations. There is also evidence from the Netherlands that the ADD users are more often cognitively impaired and frail, and they have more potential medication management problems when compared to the non-ADD users.[124] These findings are in line with the idea of

ADD as a preventive intervention targeted to patients with a higher risk of drug-related problems or inappropriate drug use. There is some evidence that ADD patients' quality of pharmacotherapy may be improved by regular medication reviews integrated with ADD.[117] There is also some evidence that ADD may pose a risk of continuing the drug treatment unchanged once a patient is enrolled to the ADD service.[50] These aspects support the idea that medication review should be integrated as a part of the ADD procedure to identify and solve inappropriate drug use. However, none of the studies included in the reviews indicated whether the standard ADD procedure applied involved a medication review to assure appropriateness of the dose dispensed medications. In Finland, the Association of Finnish Pharmacies and the national guideline on ADD (published 2016) have recommended that each patient's medications should be reviewed in the community pharmacy before they are enrolled in the ADD service.[32,37] The Ministry of Social Affairs and Health has recommended that medications for older adults should be reviewed at least once a year.[33]

Outcome measures associated with costs were missing from all the studies. In future studies, it would be essential to estimate costs and benefits from different stakeholder points of view. These stakeholders include healthcare decision-makers and providers, patients and relatives, community pharmacies, and public insurance. When ADD systems are implemented in primary healthcare, it is also important to identify what kind of changes these systems make in nurses' duties and allocation of working time, since they are mainly responsible for the distribution and administration of medicines to patients in home-care services and nursing homes. Evidence from hospital settings indicates that changes in the work process can lead to new kinds of medication errors.[141-143] For example, nurses may check the medicines less carefully because they rely on automation. Therefore, it is vital to involve parties of the medication process in the ADD implementation process. The work processes after implementation of ADD should be assessed to ensure their safety in primary healthcare.

Even though the evidence for the benefits of the ADD service in primary healthcare is limited, the service is officially implemented and widely used in the Nordic countries and the Netherlands. Perhaps because of the urgent need to find strategies and tools to ensure the safe use of medicines in a rapidly growing elderly population.

6.2 INITIATION PROCESS OF THE AUTOMATED DOSE DISPENSING SERVICE (II)

The results of Study II indicate that the medications are not always appropriate before the patients are enrolled in the ADD service. Further, the

patients' medication lists are not always up to date, both of which are crucial for medication safety. On the other hand, it seems that the initiation process of the ADD service varies between the community pharmacies and further development and standardisation of the process are needed.

A medication review is an important part of the ADD service from the medication safety point of view.[117] The results of Study II indicate that some type of medication review was conducted for almost all patients enrolled in the ADD service. However, the results revealed that the methods varied in the reviews conducted, and physicians were not always involved in the review process. There is evidence that during a medication review conducted by a pharmacist, DRPs could be recognized and solved in collaboration with a physician.[105,106,110,144] In Finland, it is recommended that a medication review is conducted when the ADD service is initiated.[32,37,38] In Study II the respondents indicated that a prescription review was the one most commonly conducted. It is the least comprehensive of the medication reviews and can be conducted by a pharmacist without contacting the physician.[100,132] Results also indicate that community pharmacists spent only a bit more than half an hour in reconciling the medication list and reviewing the medication. Thus, among the respondents, there might be confusion in definitions between the prescription review and the medication review since the physician was reported to be involved in more than half of the reviews.

The findings of Study II indicate that more detailed instructions for conducting the medication review are needed. This inquiry also concerns the coordination of collaboration in conducting medication reviews. It was found that even in a prescription review, which could be conducted by an individual healthcare professional, two to four organizations were involved. Effective use of resources is essential, since the proportion of elderly people is increasing, and thus, the collaboration of physicians, pharmacists, and other healthcare professionals needs further development.[105,106,145,146] Controlled intervention studies on the impact of different levels of medication reviews and the quality of ADD users' drug therapy are needed.

The results of Study II also suggest that patient medication lists are not always up-to-date and that information on medication must be gathered from multiple sources. There is evidence that inaccuracies in the medication lists could harm the patient.[147,148] A medication reconciliation might reduce medication discrepancies, potential adverse drug events, and adverse drug events.[92-95] There is also evidence that pharmacist involvement in the medication reconciliation processes ensure effective and successful outcomes of the process.[92,94] Thus, medication reconciliation is an important part of the ADD service that could enhance medication safety.[139] The medication list reconciling process must be coordinated and working properly, including also consistent methods for informing the community pharmacy of changes to

medication. The importance of up-to-date medication lists is acknowledged in the national level in Finland and development project is ongoing.[25,26] The project aims to achieve a national up-to-date medication list for each patient which is available for the patients themselves and all health professionals who need information in the care process.

When the ADD service is considered in the light of James Reason's risk management theory, the service can be seen as an additional systematic defence in the medication use process for patients with complex long-term medications to reduce risk of harm.[40,41] Our findings provide evidence that medication reconciliation and medication review are essential parts of the ADD to prospectively influence safety of the medications. If medication reconciliation and medication review are not included in the ADD service, the service is just a technical procedure to provide medicines in dosing pouches. This might lead to prolonged inappropropriate drug use. It might also lead in to a situation where drugs that are meant to be used as-needed are used regularly (e.g. hypnotics). If medication reconciliation and medication review are not included in the ADD service, the service could paradoxically be harmfull for the patients instead of an additional systematic defence in the medication use process. The ADD service needs to be seen as a procedure that includes medication reconcialition and medication review to ensure safety of the service. More research is needed from the medication safety point of view to optimize and standardize the ADD service procedure.

After Study II was completed in 2014, a more comprehensive guideline of the good practices for initiating the ADD service has been published by the Ministry of Social Affairs and Health in 2016.[37] In this guideline the ADD process has been further standardised. In this standardisation, the results of the studies I and II were utilized, which were published at the time the guideline was compiled. However, implementation of this guideline is not studied.

6.3 AUTOMATED DOSE DISPENSING SERVICE'S IMPACT ON MEDICATION USE AND QUALITY (III AND UNPUBLISHED STUDY)

Drug use

Study III is the first nationwide controlled intervention study on the influence of ADD on drug use in primary care patients. The study findings suggest that initiating ADD decreased drug use during a one-year observation period. The decrease was found in more than half of the top 20 active substances used. Two of these drugs, temazepam and zopiclone, are potentially inappropriate

hypnotics for geriatric patients.[69-71,75,85] ADD service patients also had more starts and discontinuations in their drug use than matched control patients.

The decrease in drug use may be related to two of the ADD service's characteristics. A prescription review conducted and reduced amount of the drug wastage. First, the ADD procedure in Finland includes a prescription review for each patient before the enrolment. At a minimum, doses, duplications and drug-drug interactions are checked during the prescription review (Study II). As a consequence, this may lead to a reduction in drug use, as suggested by findings of this study.

Another reason for the reduced drug use in the ADD group may be reduced drug wastage, compared with the standard dispensing procedure because, in ADD, drugs are dispensed for a period of 14 days. Normally in Finland, drugs are dispensed for a maximum of three months in packages of 30 or 100 tablets. If a drug is discontinued for a patient having the ADD service, only a maximum of two weeks' drug supply is wasted. In the standard dispensing procedure, the wastage could be up to three months' supply, i.e. six times more.

If the medication review is appropriately conducted, it should also lead to qualitative changes in the individual patient's medications in those cases with potentially inappropriate medications. In Study II it was found that changes in patients' drug regimens were made. These changes were made due to treatment-related reasons or technical reasons. In this study (III), the changes in drug use quality were indicated by the fact that hypnotic use was more often started and discontinued in the ADD service group. The daily doses of zopiclone and temazepam were also reduced. They are both medicines that should be avoided or at least their use should be limited to a minimum in older people, due to their short-term and long-term adverse effects.[69-71,75,85] Still, they are quite commonly used among older primary care patients.[66]

Starts and discontinuations observed in drug use may partly be artefacts, rather than actual events. These are related to the reimbursement system since it does not cover all medicines and package sizes. In ADD, reimbursed medicines are favoured, and non-reimbursable medicines are changed to reimbursable ones. If non-reimbursed medicines are dispensed before the ADD service initiation and reimbursable medicines after it, this would appear to indicate a change (start) in the register data, including only reimbursed medicines. Thus, the register data may be lacking some of the data needed to evaluate the impact of the ADD service on the appropriateness of the drug use.

Quality of drug regimens

The results imply that the quality of the drug regimens may be improved after initiation of the ADD service when the quality of drug use was measured by

explicit inappropriate drug use criteria in primary care patients ≥65 years compared to matched controls in the one-year cohort study. The risk of use of inappropriate drugs was lower after the ADD service was initiated when measured with the Beers criteria.[85] However, when the quality of drug use was measured with more complex criteria, such as concomitant use of potentially inappropriate drugs, the quality of drug use may not be improved. The risks of use of ten or more drugs and three or more psychotropic drugs were higher after initiation of the ADD service.

The results of Study II reveal that a medication reconciliation and a medication review are performed as a part the ADD service. However, a prescription review was the most commonly conducted type of review, which is the least comprehensive of the medication reviews available.[100,132] As a consequence, it seems that only simple problems in the patients' medication could be solved with this medication review. The results imply that simple problems, such as the elimination of a single inappropriate drug from patients' drug regimen, could be solved.

Previous studies and the study III imply quite evidently that patients enrolled in the ADD service suffer severe nervous system diseases, and they have complex drug treatments with multiple medications.[17,49,110,113,116] The results of this unpublished study imply that more complex problems, such as concomitant use of three or more psychotropics, could not be solved with a review used as a part of the ADD service. Furthermore, in previous studies, it was found that the number of drugs may increase after initiation of ADD.[114,116] Thus, it seems that a more comprehensive medication review than the review used should be implemented as a part of the ADD service. The medication review should be conducted regularly, not only as a part of the initiation process of the ADD service.[37] If the review is not sufficient and not performed regularly, it may lead to inappropriate drug use and inappropriate polypharmacy. Currently, in Finland, most of the prescriptions are valid for two years at the time,[149] and thus, the interval between contacts to a physician may get longer. This approach may elevate the risk that patients' drug regimens are not reviewed regularly.

As shown in this unpublished study, there is also further evidence that potentially inappropriate medication (PIM) use is common among Finnish ADD users and it is not decreased during six month follow-up period after initiation of the service.[114] In addition to this, the number of used drugs was increased after the ADD service was initiated. In another Finnish study investigating outcomes of a collaborative medication review, the use of PIMs, excessive use of psychotropics, and high anticholinergic and serotonergic load were common, although most of the patients were using ADD.[110] In this study, practical nurses made preliminary medication risk assessment for the patients,[150] and a pharmacist performed a prescription review prior a triage

meeting with a patient's physician. The results of this randomized controlled trial indicated that more optimal medication review model is needed to solve complex problems in patients' drug regimens.

When the ADD service is initiated for a patient, the physician responsible for the patient's care is in a crucial part in ensuring that the patient's drug regimen is appropriate. Further research is needed on optimal practices to ensure that ADD users drug use is appropriate.

6.4 RELIABILITY AND VALIDITY OF THE RESEARCH METHODS

Study I

The major limitation of Study I is the low number of eligible studies and low methodological quality of the existing studies. The studies that passed the inclusion criteria had weaknesses in the study designs, sampling, and research methods, hindering the generalisation of the findings. Only three studies were controlled cohort studies,[50,129] even though controlled studies provide more evidence for the outcome of the intervention.[151] Other studies were uncontrolled cohort studies or descriptive studies. The literature search was restricted to starting from the year 1995. However, in a narrative search done before the systematic search, studies from the late 1980s and early 1990s were not found, because the earliest time the ADD service was launched in primary healthcare was in the late 1980s in Sweden.[35]

Study II

In Study II, there may be local or regional variation between ADD initiation processes which were not possible to identify with the limited sample of pharmacies used in this study. The response rate of this study was rather low (45%), which may cause non-response bias. Pharmacists who conducted the ADD service initiation process according to the recommendations may have responded more actively than the other pharmacists. Also, the time-consuming self-report, which consisted of an abundance of questions, may have influenced the response rate. The pharmacists were advised to respond via the Internet or by mail. Other studies conducted in the Finnish community pharmacies via the Internet have yielded response rates of 20–30%, while mail surveys have yielded 50–60%.[152,153] The response rate for this study was within this range.

Study III and unpublished study

The main strength of these register-based studies is the controlled cohort study design that was applied. Patients' gender, age, area of residence and the number of drugs dispensed were used as matching criteria for the study and control groups. Moreover, the number of patients' diseases was controlled in the statistical analysis. Another strength of the study is that the data were collected from the Finnish Prescription registry that covers all reimbursed prescription drug purchases for ambulatory care patients living in Finland.[135] All permanent residents of Finland are entitled to have their drug costs refunded. The reimbursement system remained the same during the study period of 2006–2008. Thus, drug use changes or changes in the quality of drug use could not be explained by fundamental changes in the reimbursement system.

The register data used in the studies were routinely collected for administrative purposes, and thus, they do not necessarily represent the actual drug use in primary care. The data do not include drug use in institutions, over-the-counter drugs and drugs that are not reimbursed, e.g. small packages of some medicines. The fact that only reimbursed products were included in the register could have resembled an increase in drug use, especially in the study group, since reimbursed products are favoured in ADD. However, this study found that drug use decreased in the study group.

An important issue that should be remembered when interpreting the results of this study is that the patients using the ADD service were a highly selected patient group. Despite the matching, the prevalence of chronic diseases was higher in the study than in the control group. This fact may be explained by the fact that ADD patients suffer more often from severe central nervous system diseases, leading to complicated drug combinations. [17,49,110,113,116] Therefore, drug consumption could be expected to be higher and quality of drug regimens lower in the study than in the control group. However, drug consumption decreased in the study group after ADD initiation.

On the other hand, the outcomes for the quality of drug use were not entirely positive. In the future studies exclusion of the Alzheimer's disease patients and patients suffering severe mental diseases (e.g. psychoses) should be considered since drug use in these patient groups might be quite different compared to patients not suffering from these diseases. This exclusion might add the reliability of the results regarding drug use as well as drug use quality. The patients in the study and control groups might also be quite different as users of health services since patients using the ADD service had more chronic diseases and starts or discontinuations in their drug use compared to their matched controls.

The Beers criteria were used to measure the quality of drug use.[85] However, only one-third of the drugs included in the criteria were suitable for this register study. At the time this study was performed, the national criteria to measure the quality of drug use in older adults were not available. Thus, Beers criteria were applied. Beers criteria are widely used internationally and updated regularly.[75,83] The Swedish Indicators for Good Medication Use Among Elderly was also applied in this study.[53] The criteria are Swedish, and these criteria are applied in quite many studies investigating the quality of drug use among ADD users.[17,47-49,116] Furthermore, the lists of the long-acting benzodiazepines and anticholinergics were complemented by the lists published in Finland.[54] Thus, the quality of drug use was measured with a quite wide range of criteria.

As mentioned above, the ADD users are a highly selected patient group. The prevalence of chronic diseases was higher among the study group and ADD users suffer more often from severe central nervous system diseases. Furthermore, more patients in the control group are suffering from glaucoma and chronic asthma or other chronic obstructive pulmonary diseases. For these diseases dosage forms (e.g., eye preparations and preparations for inhalation) not suitable for ADD are used. Thus, these patients groups might have been underrepresented in the study group. The results possibly had been more reliable if the study and control group had been matched by disease group. The number of chronic diseases was planned to be used as one of the matching criteria. However, it was not possible to apply the number of chronic diseases as matching criteria since finding enough matching control patients was difficult. Thus, the number of chronic diseases was used as a covariate in the statistical analysis to enhance the reliability of the results.

Strict matching and exclusion criteria were applied. For each patient in the study group, one control patient was chosen according to matching criteria. The study group was a selected patient group and thus controls for all patients were not found. If a control patient was not found, the patient from the study group was removed. This fact might cause selection bias in the results. Strict exclusion criteria were also applied in this study. These criteria caused a 15% reduction in the study population. However, most of the excluded patients (9%) were patients under 65 years old. This exclusion was made since the focus of the studies was on older adults. In the future, it might be useful to study ambulatory care ADD service in a randomized controlled trial setting. However, this might cause ethical problems from the control patients' perspective. Thus, observational study design might be better from the ethical perspective. The controlled cohort study design applied in the register-based studies gives an important contribution to the body of the ADD research. By matching, it was possible to enhance equal distribution of the variables that might confound the results regarding the drug use and the quality of drug regimens.[134]

6.5 PRACTICAL IMPLICATIONS

In order to ensure safe and appropriate medication use of the ADD users', medication reconciliation and medication review need to be implemented more solely as a part of the service in Finland. Since the studies of this thesis have been performed, the more comprehensive guideline on good ADD practices has been published in 2016.[37] However, this is only a guideline for the stakeholders of the ADD process and actors are not obliged to adhere to the process suggested in the guideline. Furthermore, the implementation of the guideline has not been studied. Especially processes regarding medication reconciliation and medication review should be described in detail from the different stakeholders' points of view.

The medication list was incomplete for more than half of the patients and information on medication was gathered from multiple sources. The best solution for this problem would be that all actors in the medication process have shared information on medications which patients are using. Both information technology systems and processes in healthcare organisations need to be further developed to ensure that medication lists are up-to-date. A reconciled medication list enhances the physician's decision making when planning the patient's medication regimen. The national project coordinated by the Ministry of Social Affairs and Health, aiming to develop and implement a national up-to-date medication list is already ongoing.[25,26]

In most of the cases a prescription review was conducted for the patients enrolled in the ADD service. This review is the least comprehensive of the medication reviews available.[100,132] It is well established that patients using the ADD service have more drugs in their regimen and more potentially inappropriate drug use (e.g., concomitant use of three or more psychotropics) compared to patients using the standard dispensing procedure.[17,49,113,116] It seems that the more comprehensive medication review needs to be implemented as a part of the ADD service to ensure rational medication for the ADD users. This review might be best to be conducted in collaboration with a physician, a pharmacist and nurses who are responsible for the medication of the ADD user.[28,110]

When municipalities or healthcare providers in Finland are purchasing the ADD service by the competitive tenders, the tenders' conditions, especially qualitative conditions, need to be set in the way that medication safety of the ADD patients is ensured. The medication reconciliation needs to be required. Furthermore, the comprehensiveness of medication review needs to be acknowledged. In these competitive tenders, the service fee should not be the only crucial issue when selecting the supplier of the ADD service. The qualitative conditions need to be assessed and considered sufficiently when selecting the supplier.

6.6 TOPICS FOR FUTURE RESEARCH

Further evidence is needed to draw sound conclusions on ADD's outcomes. Further research applying relevant and robust study designs, methods, and outcome measures is needed to provide evidence for the ADD service benefits in terms of medication safety, appropriateness of medication use and medication adherence. ADD's economic evaluation was not performed, nor costs were studied in any of the studies. In future studies, the impact of ADD on medication costs and its impact on healthcare resources utilization should also be estimated.

The implementation of the national guideline on good practices on ADD is not studied.[37] The start-up process of the ADD service needs further development to ensure a standard procedure in terms of medication reconciliation and medication review for each patient and optimal use of the healthcare resources. Further research should be focused on this area to optimize the ADD procedure from the inappropriate drug use perspective. The medication review procedure should be optimized as a part of the ADD procedure. Further studies should explore ADD's impact on drug use as well as on the quality of drug use in more detail, e.g., on long-term impacts.

The ADD service is quite widely used in some other countries. The procedures applied in ADD in other countries should be benchmarked in order to implement possible good practices in Finland.

When municipalities or healthcare providers are purchasing the ADD service, the competitive tenders' conditions (both qualitative and quantitative) should be audited and evaluated from the perspective of safe medication use. Moreover, the conditions in which the purchase decisions are based on should be investigated. These studies are crucial in order to ensure the safety and quality of mediations in the ADD service and to decrease possible preventable costs related to unsafe practices.

7 CONCLUSIONS

- The systematic literature review reveals that few controlled cohort studies and no randomized controlled studies have explored ADD in primary care. Consequently, the evidence for ADD's influence on appropriateness and safety of medication use is limited and lacking on costs and cost-effectiveness.

- When the ADD service was initiated, the medication list was incomplete for more than half of the patients and information on medication was gathered from multiple sources. Thus, results imply that the quality of the patients' medication charts is enhanced during initiation of the ADD service. Some type of medication review was conducted for most of the patients, most commonly a prescription review, which is the least comprehensive type of medication reviews. The review was less comprehensive even though the previous studies suggest quite evidently that patients using the ADD have more inappropriate drugs in their regimens than patients using the standard dispensing procedure.

- The results of this thesis suggest that drug use may be decreased after initiation of the ADD service. The decrease in drug use may be related to two of the ADD service's characteristics: a prescription review conducted and reduction of the drug wastage. Furthermore, the register-based study reveals that there were more starts and discontinuations on drug use among ADD users.

- The ADD users drug regimens quality may be enhanced by simple improvements. When explicit inappropriate drug use criteria measured the quality of drug use, an improvement was found. This improvement may be related to medication reconciliation and a medication review conducted when initiating the ADD service. However, more complex problems in the drug regimens could not be solved. When the quality of drug use was measured with more complex criteria, such as concomitant use of potentially inappropriate medicines drugs, the quality of drug regimens was not improved. The implications for qualitative changes in drug regimens were also found in the survey. Almost half of the patients had treatment-related changes in their medications.

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APPENDICES

Appendix 1

Search strategy for the Medline.

Ovid MEDLINE(R)
1. automated medication dispens*.ti,ab. (20)
2. automated medication distribut*.ti,ab. (6)
3. automated drug distribut*.ti,ab. (5)
4. automated drug dispens*.ti,ab. (14)
5. automated dose-dispens*.ti,ab. (3)
6. automated dose distribut*.ti,ab. (0)
7. automated dispensing system*.ti,ab. (29)
8. multidose drug dispens*.ti,ab. (0)
9. multi-dose drug dispens*.ti,ab. (2)
10. multidose drug distribut*.ti,ab. (1)
11. multi-dose drug distribut*.ti,ab. (1)
12. unit-dose dispens*.ti,ab. (45)
13. unit-dose distribut*.ti,ab. (33)
14. (automat*adj2 (dispens*or distribut*)adj2(device* or system* or scheme*)).ti,ab. (96)
15. (automat* adj2 dose dispens*).ti,ab. (7)
16. (automat* adj2 dose distribut*).ti,ab. (10)
17. ((multidose or multi-dose) adj2 dispens*).ti,ab. (8)
18. ((multidose or multi-dose) adj2 distribut*).ti,ab. (5)
19. (unit-dose adj2 (dispens* or distribut*)).ti,ab. (218)
20. or/1-19 (350)
21. (news or letter or comment or editorial or interview or historical article).pt. (1438428)
22. 20 not 21 (338)
23. limit 22 to yr=”1995-current

Appendix 2

The Beers criteria published 2012.[85]

Available and suitable for this register study
Amitriptyline, Chlordiazepoxide-amitriptyline, Clidinium-chlordiazepoxide, Clomipramine, Clonidine (as first-line antihypertensive), Digoxin (>0.125mg/d), Dipyridamole (oral short-acting), Disopyramide, Doxepin (>6mg/d), Ergot mesylates, Estrogens with or without progestins (avoid oral use and topical patch, intravaginal use accepted), Hydroxyzine, Indomethacin, Ketorolac, Meprobamate, Metoclopramide, Nifedipine (immediate-release), Orphenadrine, Perphenazine-amitriptyline, Prazosin (avoid as an antihypertensive), Trimipramine
Available, not suitable for this register study
Belladonna alkaloids, Amiodarone (as first-line treatment of atrial fibrallation), Antipsychotics (first and second generation, avoid use for behavioural problems of dementia), Benzodiazepines (any type, avoid for treatment of insomnia, agitation or delirium), Dronedarone (as first-line treatment of atrial fibrallation and patients with permanent atrial fibrallation or heart failure), Flecainide (as first-line treatment of atrial fibrallation), Growth hormone, Ibutilide (as first-line treatment of atrial fibrallation), Insulin (sliding scale alone), Methyltestosterone and testosterone (avoid unless indicated for moderate to severe hypogonadism), Mineral oil, Nitrofurantoin (long-term suppression), Non-COX-selective NSAIDs (avoid chronic use unless other alternatives are not effective and patient can take gastroprotective agent), Nonbenzodiazepine hypnotics (avoid chronic use >90 days), Propafenone (as first-line treatment of atrial fibrallation), Quinidine (as first-line treatment of atrial fibrallation), Scopolamine, Sotalol (as first-line treatment of atrial fibrallation), Spironolactone (>25mg/d, avoid in patients with heart failure or with a CrCl<30 ml/min)
Not available in Finland
Amobarbital, Benztropine, Brompheniramine, Butobarbital, Butalbital, Carbinoxamine, Carisoprodol, Chloral hydrate, Chlorpheniramine, Chlorpropamide, Chlorzoxazone, Clemastine, Cyclobenzaprine, Cyproheptadine, Desiccated thyroid, Dexbrompheniramine, Dexchlorpheniramine, Dicyclomine, Diphenhydramine (oral), Dofetilide, Doxazosin, Doxylamine, Glyburide, Guanabenz, Guanfacine, Hyoscyamine, Imipramine, Isoxsuprine, Megestrol, Meperidine, Mephobarbital, Mesoridazine, Metaxalone, Methocarbamol, Methyldopa, Pentazocine, Pentobarbital, Phenobarbital, Procainamide, Promethazine, Propantheline, Reserpine, Secobarbital, Terazosin, Thioridazine, Ticlopidine, Trihexyphenidyl, Trimethobenzamide, Triprolidine