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MERVI RANTSI

Health economic evaluation of implementation strategies for reducing inappropriate medication use in older people with dementia

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Author's address: Department of Health and Social Management
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Supervisors: Postdoctoral Researcher Virva Hyttinen, Ph.D.
Department of Health and Social Management
University of Eastern Finland
KUOPIO
FINLAND

Research Director Eila Kankaanpää, Ph.D.
Department of Health and Social Management
University of Eastern Finland
KUOPIO
FINLAND

Reviewers: Professor Mika Kortelainen, Ph.D.
Department of Economics
University of Turku
TURKU
FINLAND

Professor Maria Nuotio, M.D., Ph.D.
Department of Clinical Medicine
University of Turku
TURKU
FINLAND

Opponent: Research Consultant Ties Hoomans, Ph.D.
Care Policy and Evaluation Centre
London School of Economics and Political Science
LONDON
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ABSTRACT

The aim of this dissertation was to evaluate implementation strategies for reducing potentially inappropriate medications (PIMs) in older people with dementia using economic evaluation and quasi-experimental study designs. Evaluation is integral to the field of implementation science, aiming to understand the processes and factors associated with knowledge translation in a healthcare setting. Evaluation produces information on the key outcomes to which attention should be paid during the implementation of evidence-based practice (EBP) and de-implementation of low-value care.

This dissertation consists of four Articles. First, we conduct a scoping review to find gaps in this research area. Second, we evaluate the cost-effectiveness of an educational intervention to recognize PIMs and adverse drug events for nurses in assisted living facilities in Helsinki. Third, we use interrupted time series (ITS) design to examine the relationship between the publication of the Finnish Current Care Guidelines on Memory Disorders and the trends of psychotropic use among community-dwelling Finnish people aged ≥65 and who had purchased anti-dementia medication. Fourth, we analyse the physician peer network influence before and after the publication of the guidelines using a fixed-effect

model with physician fixed effects. In Articles III and IV, we use nationwide Finnish register data on dispensed medicines reimbursable under the National Health Insurance (NHI) scheme.

Our scoping review revealed that the evaluations of implementation strategies took place at the initial stages of the process, while evaluations on sustainability and implementation cost-effectiveness were rare. An educational intervention, effective at reducing PIMs in assisted living facilities, was estimated to be less costly and less effective from healthcare perspective, measured in quality adjusted life years (QALYs), than treatment as usual. The publication of the Finnish Current Care Guidelines on Memory Disorders was not associated with changes in the trend of psychotropic use, but a more favourable association was found with the trend of new users of psychotropics. Lastly, we found that both the publication of the Finnish Current Care Guidelines on Memory Disorders and the physician peer network had an influence on new prescriptions of psychotropics. However, the influence from peer networks was unchanged after the guidelines were published.

Collectively, this dissertation suggests that economic evaluation and quasi-experimental study designs are feasible in the evaluation of implementation strategies. This dissertation informs health policy decisions aimed at improving the quality of dementia care. The findings indicate that clinical guidelines and consensus among healthcare professionals may facilitate the de-implementation of low-value prescriptions for people with dementia. In future, implementation science would benefit from investigating empirically the causal mechanisms through which implementation strategies affect treatment outcomes.

Keywords: Implementation, de-implementation, clinical guidelines, guideline adherence, health economics, evidence-based practice, low-value care, potentially inappropriate medication, dementia, memory disorders, peer network, behavioural and psychological symptoms of dementia, quasi-experimental designs, registry-based research, economic evaluation, cost-effectiveness, cost-utility, scoping review

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Implementointistrategioiden taloudellinen arviointi – vältettävien lääkkeiden käytön vähentäminen muistisairailla iäkkäillä.
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TIIVISTELMÄ

Tässä väitöskirjassa arvioidaan implementointistrategioita, joiden tavoitteena on vähentää vältettävien lääkkeiden käyttöä muistisairailla iäkkäillä. Tutkimuksessa hyödynnämme taloudellisen arvioinnin ja kvasikokeellisen tutkimuksen menetelmiä. Implementoinnin arviointitutkimus on osa implementaatiotutkimusta, jossa pyritään ymmärtämään tutkimustiedon leviämistä käytännön työhön terveydenhuollossa. Implementoinnin arvioinnilla tuotetaan tietoa keskeisistä tekijöistä, joihin tulisi kiinnittää huomiota näyttöön perustuvien käytäntöjen implementoinnissa ja vähähyötyisistä hoitokäytännöistä luopumisessa (de-implementoinnissa).

Ensiksi toteutamme kartoittavan katsauksen löytääksemme tutkimusaukot tällä tutkimusalalla. Toiseksi arvioimme koulutusintervention kustannusvaikuttavuutta. Arvioitava koulutusinterventio on tehostetun palveluasumisen hoitohenkilökunnalle Helsingissä järjestetty koulutus, joka käsitteli iäkkäillä vältettävien lääkkeiden ja niiden aiheuttamien haittavaikutusten tunnistamista. Kolmanneksi käytämme keskeytettyä aikasarja-analyysiä selvittääksemme, onko Muistisairauksien Käypä hoito -suosituksen julkaisulla vaikutusta psyykenlääkkeiden käytön trendeihin väestötasolla. Neljänneksi käytämme

kiinteiden vaikutusten mallia ja tutkimme ovatko hoitosuosituksen julkaisu ja lääkäreiden vertaisverkosto yhteydessä psyykenlääkkeiden määräämiseen. Tutkimuksissa kolme ja neljä käytämme aineistona Kelan tilastoa sairausvakuutuksesta korvattavista lääketoimituksista.

Katsauksemme mukaan implementoinnin arviointia on aiemmin tehty implementointiprosessin alkuvaiheissa, kun taas jatkuvuutta ja implementointistrategioiden kustannusvaikuttavuutta koskevat arvioinnit olivat harvinaisia. Tutkimuksemme mukaan koulutusintervention terveydenhuollon kustannukset olivat matalammat mutta tulokset laatupainotetuissa elinvuosissa (quality adjusted life years, QALY) mitattuna olivat heikommat verrattuna tavanomaiseen hoitoon. Muistisairauksien Käypä hoito -suosituksen julkaisemisella ei ollut yhteyttä psyykenlääkkeiden käytön trendin muutoksiin, mutta psyykenlääkkeiden uusien käyttäjien trendi oli hieman laskeva hoitosuosituksen julkaisun jälkeen. Lopuksi havaitsimme, että Käypä hoito -suosituksen jälkeen psyykenlääkemääräykset vähenivät. Paljon psyykenlääkkeitä määrännyt vertaisverkosto oli yhteydessä kohonneeseen määräämiseen, eikä hoitosuosituksen julkaisu muuttanut verkoston yhteyttä määräämiseen.

Väitöskirjassa havaitaan, että taloudellisen arvioinnin ja kvasikokeellisen tutkimuksen menetelmät ovat soveltuvia implementointistrategioiden arviointiin. Väitöskirjan tuloksia voidaan hyödyntää muistisairauksien hoidon laadun edistämisessä sekä tulevissa implementointitutkimuksissa. Tulokset osoittavat, että hoitosuositukset ja terveydenhuollon ammattilaisten yksimielisyys voivat yhdessä edistää vähähyötyisistä lääkehoidoista luopumista muistisairauksien käytösoireiden hoidossa. Tulevaisuudessa implementointitutkimus hyötyisi kausaalisten mekanismien empiirisestä tutkimuksesta.

Avainsanat: Implementaatio, implementointistrategiat, hoitosuositukset, näyttöön perustuva käytäntö, de-implementointi, terveystaloustiede, vähähyötyinen hoito, iäkkäillä vältettävät lääkkeet, muistisairaudet, vertaisverkosto, käytösoireet, rekisteritutkimus, kvasikokeellinen tutkimus, taloudellinen arviointi, kustannusvaikuttavuus, kartoittava katsaus

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Among other researchers across various fields of science, I have been intrigued by the influence of peers on individuals' behavior. This fascination has its roots in my personal experiences, particularly during my time in the WELMA doctoral program, where I gained invaluable insights into the significance of peer networks and their empowering influence on PhD students. It is time to express my gratitude to my peer networks.

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Kuopio November 3, 2023
Mervi Rantsi

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15D	The 15-dimensional instrument
ARIMA	Autoregressive Integrated Moving Average
ATC	Anatomical Therapeutic Chemical
AUC	Area under a curve
BPSD	Behavioural and psychological symptoms of dementia
CCI	Charlson comorbidity index
CI	Confidence interval
COINS	Cost of Implementing New Strategies
cRCT	Cluster randomized controlled trials
DiD	Difference-in-Differences
EBP(s)	Evidence-based practice(s)
EPIS	Exploration, Preparation, Implementation, Sustainment framework
ERIC	The Expert Recommendations for Implementing Change
GDP	Gross Domestic Product
HILMO	The Care Register for Health Care
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITS	Interrupted time series
IV	instrumental variable
MEDIFF	MEDIFF research project: Evaluation of implementation strategies to promote rational use of medicines in older people
Meds75+	The Meds75+ database maintained by the Finnish Medicines Agency, Fimea supports the clinical decision-making on the pharmacotherapy of patients over 75 years of age
MMSE	Mini-Mental State Examination
NHI	National Health Insurance
NPS	Neuropsychiatric Symptoms
NSAID	Non-steroidal anti-inflammatory drug
OLS	Ordinary least square

PIM(s)	Potentially inappropriate medication(s)
PCC	Population/Concept/Context
PRISMA-ScR	The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
PYRS	Person-years
QALYs	Quality adjusted life years
RCT	Randomized controlled trials
STOPP/ START	Screening Tool of Older Persons' Potentially Inappropriate Prescriptions and Screening Tool to Alert to Right Treatment
SCRQoL	Social Care-Related Quality of Life
SD	Standard deviation
SE	Standard error
SF	Statistics Finland
SIC	Stages of Implementation Completion
SII	Social Insurance Institution
SNA	Social network analysis
TAU	Treatment as usual
THL	The Finnish Institute for Health and Welfare
WTA	Willingness to accept
WTP	Willingness to pay

1 Introduction

Evidence-based practices (EBPs) are crucial for effective healthcare, but they cannot change health outcomes of the population unless they are implemented into everyday practice (Eccles & Mittman, 2006). However, the implementation of EBPs in healthcare may be unpredictable, slow, and complex. Various factors, such as lack of knowledge, resistance to behavioural change, and organizational or financial constraints, can hinder healthcare professionals' adherence to guideline recommendations (Fischer et al., 2016; Grol, 2001; Grol & Grimshaw, 2003).

Additionally, not all healthcare practices are evidence-based, potentially leading to harm, unnecessary costs, and resource wastage, known as low-value care (Chandra & Staiger, 2017; Grimshaw et al., 2020). Low-value care is a global issue, with estimates suggesting that 10-30% of healthcare practices provide little or no benefit to patients, resulting in significant personal and societal costs (Kim et al., 2021; Verkerk et al., 2018). Accordingly, these practices should be de-implemented, which is defined as the abandonment of low-value care (Prasad & Ioannidis, 2014; Powers et al., 2020). Uncertainty or disagreement about low-value care, pressure from other physicians, and a desire to do something for patients are the main reasons recognized for continuing to utilize low-value care (Ingvarsson et al., 2020; Patey et al., 2021).

The process of translating evidence into practice is not straightforward, and implementation science is focused on increasing understanding of its complexity and addressing the difficulties associated with the implementation of EBPs (Bauer & Kirchner, 2020; Nilsen, 2020, p.8–31). Implementation science is defined as scientific studies aimed at enhancing the systematic uptake of research findings and the intention is related to the use of research in decision-making (Nilsen, 2015; Nilsen & Birken, 2020, p.1–6). The foundation of implementation science lies in evidence synthesis and randomized controlled trials (RCTs). Evidence-based

research and implementation research are interconnected, aiming to improve the quality and effectiveness of healthcare, leading to better health outcomes for the population (Eccles & Mittman, 2006; Grol, 2001).

Implementation science places emphasis on establishing causality, but the empirical implementation research employs mainly qualitative and observational methods to identify and describe determinants of the implementation process (Lewis et al., 2018, p.229–244; Rabin & Brownson, 2012, p.23–51). Implementation research examining economic factors of implementation process remains rare. Strengthening the role of health economics is recommended to improve economic evidence and enhance resource allocation and value in healthcare (Barnett et al., 2020, 2021; Roberts et al., 2019). Different economic theories, methodologies and applications can further inform decision-making processes and optimize implementation strategies. The general aim of this dissertation was to use economic evaluation and quasi-experimental study designs to evaluate implementation strategies for reducing potentially inappropriate medication (PIM) use in older people with dementia.

Dementia is a major global health issue affecting around 55 million people worldwide, and its prevalence is expected to increase in the future (World Health Organization, 2021). Finland is one of the most rapidly aging countries and older people more often live with dementia. Furthermore, up to 90% of people with dementia develop behavioural and psychological symptoms of dementia (BPSD), also referred to as Neuropsychiatric Symptoms (NPS), during their illness (Ballard et al., 2008; Finkel et al., 1996; Lyketsos et al., 2000; Phan et al., 2019). Psychotropic medication is prevalent in the treatment of BPSD (Jester et al., 2021; Kirkham et al., 2017); however, older people with dementia are more prone to side effects and their use of psychotropics has been associated with potential harm, including falls, fractures, and mortality (e.g., Byerly et al., 2001; Maust et al., 2015; Saarelainen et al., 2017; Schneider et al., 2005; Watt et al., 2021). Medication use in the older population is classified as potentially inappropriate if the associated risks outweigh the potential benefits, and the use of PIM should be avoided (Renom-Guiteras et al., 2015).

People with dementia may not be able to provide or utilize information as well as other patients. Consequently, dementia patients are more prone to being affected by actions taken by physicians and other healthcare professionals (Chandra et al., 2023). Clinical guidelines designed to increase the quality of care and to decrease practice variation in dementia care are reasonable from clinical and economic perspectives (Burley et al., 2020; Knapp et al., 2013). The Finnish Medical Society Duodecim published the Finnish Current Care Guidelines on Memory Disorders in 2006. The guidelines were updated in January 2017, after which they included guidance on the treatment of BPSD. The guidelines recommend non-pharmacological interventions as primary treatment for BPSD and to avoid initiation of psychotropics (Current Care Guidelines, 2017). However, the implementation of these guidelines and their relationship with inappropriate psychotropic prescriptions has not been previously investigated.

Physicians play a vital role in the successful de-implementation of psychotropics, while multidisciplinary staff is responsible for the treatment of BPSD (Kales et al., 2015). Physicians' peer networks have also been found to increase the adoption of new medicines (Agha & Zeltzer, 2022; Donohue et al., 2018; Yang et al., 2014). However, there is relatively little research on this physician peer effect and the de-implementation of inappropriate prescribing (Sacarny et al., 2019). Educational interventions, including face-to-face academic detailing and workshops for nurses, have shown promise in reducing PIM prescriptions (Loganathan et al., 2011), but economic evaluations of these strategies are scarce (Ballard et al., 2018; Sanyal et al., 2020). Although implementation and dissemination research in dementia care is comprehensive, evaluations of patient-level outcomes and the sustainability of implementation are rare (Lourida et al., 2017).

This dissertation consists of three published scientific articles (I, II, III) and one manuscript (Article IV). The implementation strategies evaluated in this dissertation were an educational intervention (Article II) and the publication of the Finnish Current Care Guidelines on Memory Disorders (Articles III-IV). We analysed the implementation of EBP in the care of older

people with dementia using cost-effectiveness analysis and quasi-experimental study designs. Articles I, III and IV are part of the MEDIFF project, which aims to evaluate the implementation of the nationwide Meds75+ database and the update to Current Care Guidelines for Memory disorders among community-dwelling older people in Finland.

First, we conducted a scoping review of the evaluations of implementation strategies on reducing PIM use in older people (Article I). With this scoping review, we aimed to find the current gaps in this research area. Second, we evaluated the cost-effectiveness of an educational intervention for nurses aimed at reducing inappropriate medication in older people in assisted living facilities in Helsinki, Finland (Article II). Third, we used Finnish register data on dispensed medicines reimbursable under the National Health Insurance (NHI) scheme (Prescription Register) to evaluate the relationship between the publication of the Finnish Current Care Guidelines on Memory Disorders (2017) and the trend of psychotropic use (Article III). Fourth, we used the Prescription Register data to analyse the physician peer network influence before and after the publication of the guidelines using a fixed-effect model with physician fixed effects. (Article IV).

This dissertation is structured as follows: Chapter 2 describes different aspects of implementation and de-implementation, as well as describes implementation strategies and the evaluation of the implementation process in order to structure the concepts of this dissertation. The focus of Chapter 3 is on the unifying and distinctive aspects of health economics and implementation science. Chapter 4 presents the dementia care setting and treatment of BPSD, as well as the need for the evaluation of implementation strategies for reducing PIM use in older people with dementia. The aim and research questions of this dissertation are presented in Chapter 5. Data and methods applied in the Articles are described in Chapter 6. The results of the Articles are presented in Chapter 7. The findings of this dissertation are discussed in Chapter 8, and Chapter 9 concludes the dissertation.

2 Implementation science

2.1 Implementation of evidence-based practices

Implementation is defined as "the process of putting to use or integrating evidence-based interventions within a setting" (Rabin et al., 2008). Specifically, implementation refers to the introduction of EBP into daily routines, requiring effective communication strategies and the removal of barriers to change (Grol & Wensing, 2020, p.3–20). Other terms used for implementation include 'knowledge translation', 'knowledge transfer', 'knowledge exchange' and 'knowledge integration' (Nilsen & Birken, 2020, p.1–6). Additionally, some closely related terms to implementation are: 1) diffusion, which refers to the natural adoption by the target group, 2) dissemination, which involves the active communication of information to stakeholders to increase their knowledge, and 3) adoption, which entails a positive attitude and decision towards change (Grol & Wensing, 2020, p.3–20).

Constantly emerging research findings that can contribute to effective healthcare cannot change health outcomes in the population unless they are adopted into practice (Eccles & Mittman, 2006). Despite the growing number of EBPs, their implementation can be unpredictable, slow, and complex. It has been estimated that about 30-40% of patients receive treatment that is not evidence-based, and 20-25% receive treatment that is either unnecessary or potentially harmful (Grol, 2001; Grol & Grimshaw, 2003). When desired benefits fail to materialize, this may be due to the lack of effectiveness of the EBP itself or a failure of the implementation process (Prior et al., 2008). The success of the implementation process may vary based on determinants (barriers or facilitators) that are related to different phases of the process (Grimshaw et al., 2012). Barriers and facilitators can be related to the EBP being implemented, the individuals expected to

adopt it, the social networks involved, healthcare organizations, and systems (Wensing & Grol, 2020, p.157–171).

Implementation is seen as a complex process. This process involves various levels, phases, contextual factors, and stakeholders, as well as their interactions (Powell et al., 2019). An implementation process occurs over time, and overlapping implementation phases are identified. The phases are categorized into exploration, preparation, implementation, and sustainment phases by the EPIS framework, which is a frequently used framework in implementation research (Moullin et al., 2019). In the exploration phase, stakeholders consider existing healthcare needs, search for EBP and assess the readiness for change. The preparation phase includes the assessment of implementation challenges and involves planning and auditing. Next is the implementation phase, where the EBP is initiated in practice, and this phase should assess evaluation, and support to reach sustainability. In the sustainment phase, the implemented EBP continues to be delivered and the desired impact is achieved (Aarons et al., 2011).

At different phases in the implementation timeline, various contexts and levels of communities are involved. In the EPIS framework, these levels are divided into system, community, organization, and individual (Ellen et al., 2011). Context is an essential part of the implementation process, closely associated with the levels of implementation. However, context lacks a unifying definition in implementation research. Some studies essentially view context in terms of a physical environment or healthcare setting and others assume that context is something more active and dynamic within the setting (Nilsen, 2015). In the latter, context is generally defined as the environmental characteristics in which implementation takes place, including interactive social networks (Dopson et al., 2008). In healthcare setting, context is typically multidimensional, multifaceted, dynamic, and complex, involving different levels, and it can be divided into outer and inner contexts. The outer context encompasses macro-level influences such as the social, economic, political, and competitive environment. The inner context includes micro- and meso-level influences, referring to the

structure, culture, history, and political contexts that shape organizations (Dopson et al., 2008; Nilsen & Birken, 2020, 1-6).

The implementation of EBP necessitates changes in the behaviour of systems, organizations, and individuals. This change in behaviour is an integral aspect of human behaviour (Francis et al., 2012). As a result, the successful implementation of EBP is said to depend on the characteristics of various stakeholders (Proctor et al., 2011). Stakeholders' characteristics influence their willingness to adopt new innovations. According to the Diffusion of Innovations theory, the most significant characteristics are beliefs, education, socio-economic status, and preferences (Rogers, 2003, 1-38). Stakeholders can be divided into four groups. The first group includes healthcare users (patients) and their families who may benefit from the implementation of the EBP. The second group consists of intervention developers who are often motivated by the desire to see their interventions used in routine healthcare and may also serve as intermediary or purveyor organizations. The third group comprises healthcare professionals responsible for delivering the EBP. Lastly, policymakers at local, regional, state, national, and international levels play a crucial role as stakeholders in the implementation process (Lewis et al., 2018, p.229–244).

2.2 De-implementation of low-value care

Healthcare practices are not always effective, or the evidence base is weak, which potentially leads to harm, unnecessary costs, or wastage of resources instead of providing health benefits. This type of care is referred to as low-value care (Chandra & Staiger, 2017; Grimshaw et al., 2020). According to a recent review, low-value care was most frequently cited as pharmaceuticals, followed by screening and medical procedures (Kim et al., 2021). Low-value care is a global issue, and it is estimated that 10–30% of healthcare practices provide little or no benefit to the patient. Consequently, low-value care may have considerable personal and societal

costs (Kim et al., 2021; Verkerk et al., 2018). In addition, low-value care may exacerbate disparities; racial and ethnic minorities, as well as lower socioeconomic groups, are at a higher risk of experiencing low-value care (Helfrich et al., 2019). Accordingly, low-value care should be minimized but de-implementation is often slow (Powers et al., 2020).

De-implementation is defined as the abandonment of healthcare practices that have been found to be ineffective and harmful (Prasad & Ioannidis, 2014). In western countries, interest in the de-implementation of low-value care within the field of implementation science has only grown in the 2010s due to the rapid development of new treatments and innovations. As a result, the term 'de-implementation' is relatively new; a search for the keyword "de-implementation" in the "Implementation Science" journal does not yield any articles before 2011. However, in 2017, seven articles were published, and in 2018, the number increased to eight (Prusaczyk et al., 2020). Furthermore, we update the search in August 2023 and the search yielded 73 articles. However, there are several other terms used for de-implementation, including 'de-adoption', 'disinvest', 'abandon', among at least 40 others (Niven et al., 2015).

While there is existing evidence regarding active interventions to implement EBP, there has been less attention focused on recommendations for de-implementing low-value care (Grimshaw et al., 2020). Evidence-based guidelines and consensus among healthcare professionals have been developed to disseminate information on low-value care (Ingvarsson et al., 2022; Patey et al., 2021; Verkerk et al., 2022). The American Board of Internal Medicine Foundation established the Choosing Wisely recommendations in 2012, which have since spread to over 20 countries. Choosing Wisely aims to develop recommendations and measure rates of overuse, with the goal of facilitating discussions between clinicians and patients about avoiding low-value healthcare. (Levinson et al., 2015). However, these initiatives do not provide specific guidance on how to de-implement low-value care or identify relevant factors for consideration. Additionally, there is a lack of economic evidence as clinical guidelines primarily focus on providing clinically relevant information

rather than cost-related details, despite the economic burden associated with low-value care (Kim et al., 2021). It is suggested that further research is needed to understand the de-implementation process and its determinants. Furthermore, additional interventions are required to address barriers and gain insights into effective strategies for achieving successful de-implementation (Grimshaw et al., 2020; Nilsen et al., 2020).

When developing strategies for de-implementation, it is worthwhile to consider that low-value care can be categorized in different ways (Prasad & Ioannidis, 2014; Verkerk et al., 2018). Prasad & Ioannidis (2014) have categorized low-value care as follows: 1) practices known to be ineffective, 2) practices with an uncertain evidence base, and 3) practices in development where the intervention may eventually be proven ineffective. In the first category, it is clear that de-implementation of the care practice should be prioritized. However, in the other two categories, the decision is more complex. The second category is the most prevalent and challenging. Prioritization should be based on the extent of the evidence base, and preference should be given to de-implementing practices that place a greater burden on the healthcare system with the least supporting evidence or highest cost. In the third category, a key consideration is taking pre-emptive steps in the implementation that allow efficient de-implementation if the intervention is eventually proven to be ineffective (Prasad & Ioannidis, 2014).

Another typology, developed by Verkerk et al. (2018), categorizes proven low-value care into three types based on the underlying reasons. These types include ineffective care, inefficient care, and unwanted care. Each type requires different approaches for successful de-implementation. In the case of ineffective care, it is important to identify patients who do not benefit from a particular treatment and limit its use. For inefficient care, which is essentially effective but delivered in an inefficient manner, reorganizing care and improving communication among healthcare providers may be key considerations for de-implementation. Unwanted care is dependent on the preferences and values of the patient, and reducing unwanted care can be achieved by facilitating shared decision-

making and improving communication between patients and healthcare professionals (Verkerk et al., 2018).

De-implementation and implementation are not entirely distinct, and the significance of understanding when and how it is appropriate to de-implement interventions is recognized to be closely interconnected with the implementation process (Brownson et al., 2015; Nilsen et al., 2020). However, the mechanisms of de-implementing low-value care and the implementation of new EBPs are somewhat different (Norton et al., 2017; Patey et al., 2021). Stakeholders play more a meaningful role in de-implementation because they need to unlearn and thus, they face different psychological and emotional processes when presented with the discontinuation of treatment, which they may even expect, than being presented with new treatments. Therefore, it is noted that de-implementation studies should prioritize the stakeholder level more widely (Prusaczyk et al., 2020). Identifying the most appropriate behaviour change techniques to specifically target barriers identified for de-implementation is said to increase the likelihood of behaviour change in practice (Grimshaw et al., 2020).

On the physician level, uncertainty or disagreement about low-value care, pressure from other physicians, and a desire to do something for patients are the main reasons recognized for continuing to utilize low-value care (Ingvarsson et al., 2020; Patey et al., 2021). In psychology, dual process models of cognition propose the following decision-making processes: 1) reflective cognition, a process based on utility, risk, capabilities, and social influences, and 2) automatic cognition, a largely unconscious process occurring in response to environment or emotions (Helfrich et al., 2018). Frequently used behaviour change techniques targeting de-implementation are: 1) behaviour substitution which aims to increase the frequency of the substitute behaviour in order to de-implement low-value care, and 2) a process of unlearning based on reflective cognition, for example, restructuring a social environment which aims to promote de-implementation by requiring physicians to get approval from a senior or

secondary physician for low-value treatment (Helfrich et al., 2018; Patey et al., 2021).

2.3 Strategies for implementing evidence-based practices and de-implementing low-value care

Implementation strategies are defined as "methods or techniques used to enhance the adoption, implementation and sustainability of a clinical program or practice" (Proctor et al., 2013). Another definition by Powell et al. (2012) posits that "an implementation strategy is a systematic intervention process to adopt and integrate evidence-based health innovations into usual care". The term 'implementation strategy' is used to refer to both single strategies and combinations of strategies. Implementation strategies are similar to clinical interventions as they involve concerted effort and action to achieve the desired outcomes. The term 'implementation intervention' is also used but there is a risk of confusing it with EBP interventions that implementation strategies are intended to support (Leeman & Nilsen, 2020, p.234–258).

Intervention and implementation are not synonyms but there are similarities and potential overlaps. The difference between a clinical intervention and an implementation strategy in healthcare can be ambiguous, especially in the case of complex interventions (Campbell et al., 2000; Lau et al., 2015; Moore et al., 2015; O'Cathain et al., 2019). However, it is clear that clinical interventions create the research evidence, the 'what' to be implemented (Eldh et al., 2017), and a key feature in implementation strategies is their aim to change knowledge, attitudes, and behaviour of stakeholders (Fischer et al., 2016; Grimshaw et al., 2012).

A variety of implementation strategies have been developed and they can be targeted to different levels or stakeholders of the implementation process. An implementation strategy should be informed by assessing barriers and facilitators of the implementation within the targeted setting (Kirchner et al., 2020). Powell et al. (2012) reviewed the literature and

through an expert consensus, they published a list of 68 discrete implementation strategies (e.g., disseminating educational materials, reminders, and audit and feedback) but most often, these were combined to form a multifaceted strategy. The strategies can be categorized in different ways, and one widely used way is based on The Expert Recommendations for Implementing Change (ERIC) compilation. ERIC implementation strategies have been clustered based on following concepts: "1) use evaluative and iterative strategies, 2) provide interactive assistance, 3) adapt and tailor to context, 4) develop stakeholder interrelationships, 5) train and educate stakeholders, 6) support clinicians, 7) engage consumers, 8) utilize financial strategies, and 9) change infrastructure" (Waltz et al., 2015).

According to previous reviews, the effectiveness of implementation strategies in different settings is studied widely but the effects have been moderate, and results remain ambiguous (Fischer et al., 2016). There is some evidence supporting the use of multifaceted interventions, interactive education, and clinical reminder systems for the effective implementation of EBP. Ineffective strategies included deductive education and passive dissemination approaches, such as posting the clinical guideline on a website or providing printed copies to healthcare professionals (Prior et al., 2008; Fischer et al., 2016). Multifaceted interventions seem to be effective strategies for implementing EBP, but the combinations of discrete strategies they involve may vary (Francke et al., 2008). Moreover, the effectiveness of multifaceted strategies is subject to uncertainties, and conducting meta-analyses has been challenging due to the wide variety of settings (Fischer et al., 2016; Francke et al., 2008; Grimshaw et al., 2004; Grol & Grimshaw, 2003; Prior et al., 2008). However, Grimshaw et al. (2004) argued that multifaceted strategies may not necessarily be more effective, and that dissemination of clinical guidelines is needed because it offers a more feasible and potentially less costly approach.

Strategies to de-implement low-value care include publishing guidelines on low-value care, education for healthcare professionals and patients,

clinical decision support, provider feedback, and financial incentives (Ingvarsson et al., 2022). A scoping review by Ingvarsson et al. (2022) used the nine implementation startegy clusters of the ERIC compilation to map strategies for de-implementation purposes and to investigate how similar de-implementation and implementation strategies are. In total, 50% of the ERIC implementation strategies were used in de-implementation studies (Ingvarsson et al., 2022). The effectiveness of de-implementation strategies is studied using different methods, but more high-quality evidence is needed (Colla et al., 2017; Ingvarsson et al., 2022; Raudasoja et al., 2022). According to Colla et al. (2017), further research is needed on, for example, pay-for-performance and risk-sharing contracts reducing the use of low-value care. A systematic scoping review of de-implementation RCTs identified 227 studies, of which most covered highly complex multicomponent strategies, and they noted that shortcomings in reporting the complexity of interventions make the repetition difficult and may increase the risk of missing important factors (Raudasoja et al., 2022).

2.4 Theories, models and frameworks of implementation and de-implementation

Implementation science has been greatly influenced by the Diffusion of Innovations theory by Everett M. Rogers, which was first published in 1962 and has its origins in sociology (Wensing & Grol, 2020, p.21–44). According to the theory, innovations spread through diffusion, which refers to the passive, untargeted, unplanned, and uncontrolled spread of innovations (Rogers, 2003, p.1–38). Moreover, implementation science applies theories of change from different scientific areas, such as psychology, sociology, educational science, communication science, organizational science, economics, and political science as well as theories, models and frameworks that have emerged from within implementation science (Nilsen, 2015; Wenging & Grol, 2020).

A scoping review by Strifler et al. (2018) identified 159 knowledge translation theories, models, or frameworks, of which 87% were used in five studies or fewer, and 60% were used only once. Most were developed for specific settings, and implementation scientists have recognized the difficulty in choosing what is most appropriate for their healthcare setting and context. Theories, models, and frameworks are used to support planning, implementation, and evaluation activities. It is suggested to be useful when applying a conceptual framework of implementation science which summarizes factors from a range of theories (Damschroder, 2020).

The terms 'theories', 'models', and 'frameworks' are often used interchangeably in implementation science. Nilsen (2015) categorizes them into five categories of theoretical approaches, as depicted in Figure 1. These five approaches serve three main purposes in implementation science: 1) describing the process of translating research into practice, 2) understanding and/or explaining what influences implementation outcomes and 3) evaluating implementation. The theories and frameworks that focus on understanding and/or explaining implementation outcomes can be further classified into determinant frameworks, classic theories, and implementation theories based on their origins, development process, and sources of knowledge they draw upon.

Theories are analytical principles that structure our observations, understanding and explanation of the world. They explain how specific relationships lead to certain events and often have predictive capacity. In implementation science, theories aim to explain the causal mechanisms of implementation, such as how healthcare professionals' attitudes and beliefs predict their adherence to clinical guidelines in practice. A model simplifies a phenomenon, focusing on specific aspects. Models and theories are closely related, with models providing a narrower scope of explanation. Unlike theories, models are primarily descriptive. In implementation science, models are often used to describe and guide the process of translating research into practice, rather than predicting or analysing factors influencing implementation outcomes. A framework serves as a structured overview or plan that categorizes descriptive

elements, such as concepts or variables, to account for a phenomenon. Unlike theories, frameworks do not provide explanations but instead describe empirical phenomena by placing them into categories. In implementation science, evaluation frameworks are often used to identify factors influencing implementation outcomes. Models and frameworks do not specify mechanisms of change; they function more as checklists of relevant outcomes in implementation (Nilsen, 2015).

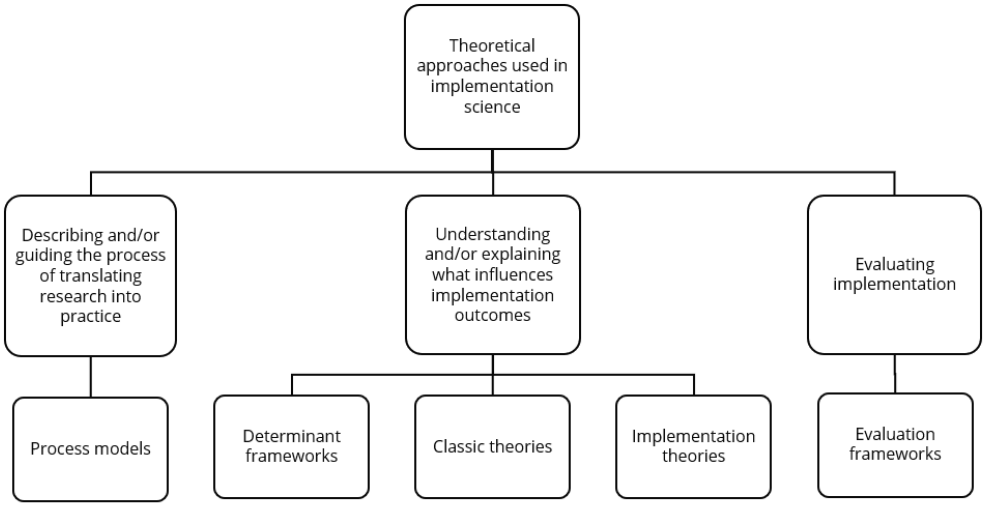

Figure 1. Aims of the use of theoretical approaches in implementation science and the five categories of theories, models and frameworks (Nilsen, 2015).

Limited theories, models and frameworks are specifically developed for de-implementation. Nilsen et al. (2020) conducted a scoping review in medical care, identifying ten studies. Among these, five presented de-implementation theories, models, and frameworks, while five applied existing implementation theories, models, and frameworks for EBPs. The de-implementation approaches included two theories, one process model, and two hybrid approaches combining elements from determinant frameworks and process models (Nilsen et al., 2020). Another scoping review by Walsh-Bailey et al. (2021) identified 27 unique models and

frameworks from public health, healthcare, and public policy. Among the 21 studies, encompassing multiple levels, the most frequent were organization and system levels. The studies included in the review often did not specify the healthcare setting or the context (Walsh-Bailey et al., 2021). It is agreed that context is critically important in implementation, however, there is a lack of consensus regarding how it should be interpreted or captured in research (Nilsen, 2015). The broad descriptions of the settings may suggest that the included theories, models, and frameworks can be applied to a wide array of contexts, but the empirical evidence is missing (Nilsen et al., 2020; Walsh-Bailey et al., 2021).

2.5 Evaluation of implementation and de-implementation

The evaluation of implementation is an integral component of implementation research (Figure 1), aiming to examine the processes and factors that contribute to successful knowledge translation. Frameworks are often used as theoretical bases to identify factors influencing implementation outcomes (Nilsen, 2015). Evaluation can take place at different phases and levels of the implementation process. Implementation frameworks may provide valuable insights into the relationship between program elements and program outcomes, offering information on critical aspects that require attention during the implementation process (Rabin & Brownson, 2012, p.23–51; Proctor et al., 2011). Frameworks provide a structure for describing, guiding, analysing, and evaluating implementation efforts (Moullin et al., 2020; Nilsen, 2015).

Process evaluation aims to describe the process of translating research into practice and explain what factors influence implementation effectiveness (Proctor, 2020, p.276–290). There are various frameworks that encompass various concepts and operationalize them to different extents. These frameworks can range from general to context- or intervention-specific and also differ in terms of comprehensiveness (Damschroder, 2020; Moullin et al., 2020). Framework developed by

Proctor et al. (2011) consists of implementation outcomes that can be applied to conceptualize and evaluate successful implementation processes in different healthcare settings.

The choice of framework can expand or limit the consideration of factors deemed important in the implementation process (Damschroder, 2020; Moullin et al., 2020). A comprehensive and general framework developed by Proctor et al. (2011) is suitable for categorizing process evaluation in various healthcare settings. This framework is utilized in several implementation evaluation studies (Proctor et al., 2023) and also to conceptualize de-implementation outcomes, identifying its similarities and differences to implementation research (Prusaczyk et al., 2020). The framework by Proctor et al. (2011) consists of eight implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation costs, penetration, and sustainability. Definitions of these outcomes are subsequently provided based on articles by Proctor et al. (2011) and Prusaczyk et al. (2020).

Acceptability refers to the perception of an EBP being favourable, and the lack of acceptability is often observed as a challenge in implementation. Unlike general service satisfaction, acceptability specifically focuses on the perception of a particular intervention. Various stakeholders, including administrators, payers, providers, and consumers, can offer insights into acceptability through methods like semi-structured interviews. In de-implementation research, the definition remains the same but the focus shifts to assessing a practice's unacceptability. If stakeholders no longer find a practice acceptable or perceive it to have low acceptability, they are more likely to consider de-implementing that practice.

Adoption, also referred to as 'uptake', is defined as the intention or action of trying an intervention. It can be evaluated from the perspective of the recipients (provider or organization) in the early or middle stages of the implementation process. When considering adoption in the context of de-implementation, it refers to the intention or initial decision to discontinue a

practice. The extent of de-adoption may vary depending on whether the intent is to completely cease the practice or reduce its use.

Appropriateness refers to the relevance or compatibility of an intervention with a specific setting, such as the perspectives of providers or consumers, or the perceived fit of the intervention within that context. Although appropriateness and acceptability are connected, it is crucial to recognize that an intervention might be seen as fitting but not inherently acceptable. For instance, an EBP could be deemed appropriate for tackling a specific condition, yet certain aspects of the implementation strategy could render it unacceptable to the provider. Appropriateness in the context of de-implementation could be conceptualized as when the stakeholder perceives the practice to not fit, have relevance, or be compatible for a given setting.

Implementation cost refers to the cost impact of an implementation effort. Implementation costs are the costs of information delivery, learning and unlearning, typically not included in economic evaluations of EBP. Different types of costs may be incurred in different stages of the implementation process (Gold et al., 2022; Hoomans & Severens, 2014). Direct measures of implementation cost are crucial for comparing the cost-effectiveness of different implementation strategies. Low-value care can be a target of de-implementation because it is costly or not cost-effective. In this context, the costs associated with the low-value practice to society and the potential savings from discontinuing the practice should be considered. However, it is essential to acknowledge that de-implementation strategies may also incur new costs.

Feasibility is defined as the extent to which a new EBP can be successfully carried out within a specific setting. It is often used to explain implementation success or failure, considering factors like how many participants were recruited, retained, or participated. Feasibility is related to appropriateness, but while an intervention may be appropriate for a service setting, it may not be feasible due to demands of resources or training. In the context of de-implementation, structural, organizational, or

contextual barriers may hinder de-implementation even if stakeholders personally want to discontinue the practice.

Fidelity is defined as the degree to which an EBP is implemented as intended by the intervention developers. Fidelity is often measured by comparing the original EBP and its implemented version in terms of adherence to the program protocol or the amount of program delivered. Self-reporting, ratings, direct observation, and recoding of actual encounters or provider-patient interactions can be used to measure fidelity. In the context of de-implementation, fidelity refers to the degree to which a practice is reduced for the recommended patients. In addition, removing practices that are not evidence-based can indirectly improve fidelity to EBPs by eliminating competition.

Penetration is defined as the integration of an EBP within a service setting. It can be calculated based on the number of eligible persons using a practice divided by the total number of persons eligible for the practice. Penetration is typically measured in the mid or later stages of the implementation process. In de-implementation research, penetration refers to the extent of discontinuing a practice within a service setting and its subsystems. This concept is particularly relevant for initiatives aiming to de-implement low-value care practices, such as the Choosing Wisely recommendations.

Sustainability is the extent to which an implemented EBP is maintained or institutionalized within a service setting, reflecting on its integration into all subsystems of an organization. Sustainability represents the long-term viability of an intervention as the final stage of the knowledge translation process when it becomes settled in organizations and society. In the context of de-implementation research, sustainability refers to the extent to which the discontinuation of a practice is maintained. This concept also encompasses potential inhibiting or challenging factors—structural, procedural, or societal—that may impact de-implementation efforts in the long run.

2.6 Evaluation of implementation strategies compared to the evaluation of interventions

Evaluation of implementation strategies differs from the evaluation of interventions, which is natural when noting the difference between the object of evaluation. Clinical interventions create the research evidence, the 'what' to be implemented and a key feature in implementation strategies is the "how" to implement this knowledge (Eldh et al., 2017; Fischer et al., 2016; Grimshaw et al., 2012). However, difference between an EBP intervention and an implementation strategy in healthcare may be unambiguous, especially in the case of complex interventions (Campbell et al., 2000; Lau et al., 2015; Moore et al., 2015; O'Cathain et al., 2019). Ambiguity occurs especially when evaluating the effectiveness of the intervention and implementation process (Eldh et al., 2017). Table 1 summarizes the main aspects that can be used to clarify the differences between the evaluation of intervention and implementation strategy.

In the evaluation of healthcare interventions, the setting is a clinical trial setting because RCTs are considered the most robust method of assessing the effectiveness and cost-effectiveness of interventions. Controversially, in the evaluation of implementation strategies, the setting is a real-world healthcare setting. The real-world setting makes it difficult to evaluate causal effect because random allocation is often not possible due to practical, ethical, social, or logistical constraints (Handley et al., 2018; Grimshaw et al., 2000).

Table 1. Differences and similarities between evaluation of interventions and evaluation of implementation strategies

	Evidence-based practice evaluation	**Implementation strategies evaluation**
Setting	**Clinical trial**	**Real-world healthcare**
Intervention	**What** (e.g., evidence on non-PIM use)	**How** (e.g., educational intervention, guideline publication for reducing PIM use)
Stakeholders	**Patient**	**Patient, healthcare professionals/managers, policymakers**
Outcomes	**Patient outcomes:** Clinical outcomes (e.g. mortality, ADEs) Health outcomes (e.g., QALYs) Cost-effectiveness (ICER)	**Implementation outcomes:** Acceptability, adoption, appropriateness, feasibility, fidelity, implementation costs, penetration, sustainability **Patient outcomes (population):** PIM use Health outcomes Cost-effectiveness (ICER)

The evaluations are interconnected, aiming to improve the quality and effectiveness of healthcare, leading to better health outcomes for the population (Eccles & Mittman, 2006; Grol, 2001). However, the outcomes used in the evaluations may differ. The difference is related to the implementation process and the stakeholders involved. Where in the evaluation of interventions stakeholders are patients, in the evaluation of implementation strategies the stakeholders may be patients or healthcare professionals and organizations, who may be the recipient of the implementation strategy used. However, the target population of the health benefit is the patient. (Lewis et al., 2018, p.229–244; Proctor et al., 2011). The outcomes used in implementation evaluation may be patient outcomes or implementation outcomes, such as the acceptability, appropriateness, or feasibility, measuring the performance or viewpoint of the recipients (Proctor et al. 2011).

Evaluation of implementation strategies often uses frameworks as theoretical bases to identify factors influencing implementation outcomes, aiming to explain the causal inference. However, the methods used in the evaluation of service outcomes are mainly qualitative or observational. These outcomes may produce valuable information about the process, which may affect the eventual population health outcomes, and thus, their recognition is an important part of the implementation evaluation. (Proctor et al. 2011; Proctor et al. 2023). Furthermore, it may not be a sufficient approach to focus either on evaluating the effectiveness of the intervention or exploring its implementation in real-world settings. It is proposed that evaluation of the effectiveness of an intervention and its implementation should be conducted simultaneously (Curran et al., 2012; Eldh et al., 2017).

3 Health economics and implementation science

3.1 Unifying and distinctive aspects of health economics and implementation science

Stakeholder decision-making and behavioural change are areas of interest in both implementation science and health economics. The research fields have a unified aim of better well-being for the population; however, they have some distinctive aspects and perspectives. Recent implementation literature has especially identified the importance of economic evidence in implementation research, calling for enhanced, high-quality cost-effectiveness analysis of diverse implementation strategies (Powell et al., 2019; Roberts et al., 2019). By understanding the potential costs and benefits associated with different implementation strategies, decision-makers can make informed choices to effectively allocate limited resources between different implementation strategies as well as between EBP research and implementation research (Dopp et al., 2021). Decisions regarding investment in implementation strategies should be made alongside those regarding investment in further research of EBPs, thereby also informing decision-makers about the re-allocation of funding between these activities (Hoomans et al., 2011).

Economic evaluation of implementation strategies can be mapped to the category of “evaluating implementation” in Figure 1. It is said to be crucial to comprehend the cost-effectiveness of implementing EBPs and assess the value of de-implementation strategies for low-value care (Grimshaw et al., 2020; Hoomans & Severens, 2014). However, there is a distinction between evaluating the cost-effectiveness of an intervention and assessing the cost-effectiveness of implementing EBP (Table 1). Economic evaluation provides comparative information of effectiveness and costs to support decisions of resource allocation by synthesizing data

from various sources, offering explicit estimates of the long-term costs and benefits of alternative implementation strategies. Economic evaluation addresses the uncertainties around costs and benefits to help decision-makers choose between implementation strategies (Grimshaw et al., 2020; Hoomans & Severens, 2014). However, the ability of economic evaluation to consider the aspects of a complex implementation process is limited (Dopp et al. 2019).

In the economic evaluation of interventions, the economic good is usually a treatment, for example medicine, and information is mainly related to the uncertainty of alternative interventions in healthcare (Drummond et al, 2015, p.19–40). However, in the evaluation of implementation strategies, information is considered the object, with the focus being on the process of 'how' to implement EBP (Table 1). Knowledge, when considered as an economic good, encompasses information, skills, expertise, and insights that hold value and can yield economic benefits. A fundamental distinction is that knowledge lacks a physical form, which makes it more challenging to measure. Moreover, the utilization of knowledge can result in positive spillover effects, benefiting individuals and organizations beyond those directly involved in the creation of new knowledge (Foray, 2004, p.1–21). This can introduce additional challenges in evaluating the cost-effectiveness of implementation strategies.

Behaviour change is another unifying interest of implementation research and health economics, and behavioural economics has been proposed as a suitable approach for implementation research (Barnett et al., 2020, 2021; Beidas et al., 2021). Literature in health economics has aimed to explain variations in physicians' practice styles and increase understanding of the determinants of treatment choices (Chandra et al., 2011; Mcguire, 2000; Phelps, 2000). Theories on physician decision-making and behavioural economic theories can be mapped to the category of "understanding and/or explaining what influences implementation outcomes" (Figure 1). The application of principal-agent theory suggests that physicians' choices depend on the benefit to the patient, the fee the

physician earns, and other situational factors (Chandra et al., 2011). Research on situational factors has focused on physicians' beliefs and knowledge about the efficacy of treatment and physicians' treatment choices (Chandra et al., 2011; Mcguire, 2000; Phelps, 2000). The principal–agent theory is widely used in the research of healthcare provision (Chandra et al., 2011; Mcguire, 2000; Phelps, 2000), but it could be utilized more concerning the implementation of EBPs (Miraldo et al., 2019).

However, it is proposed that traditional financial incentives alone may not be sufficient to drive desired healthcare outcomes and preferences may as well influence clinical decisions (Emanuel et al., 2016). Human behaviour often challenges the assumptions of rationality in traditional economic theories. Behavioural economics, highlighted by Kahneman & Tversky (1979), recognizes the impact of decision-making under uncertainty and an individual's limited ability to process all available information. Behavioural economics-informed interventions have been employed to change physician behaviour, and it was found in a recent review that changing default settings and providing social reference points were potentially effective in changing prescribing behaviour, particularly to de-implement of low-value prescribing, but more research in this field is needed (Wang & Groene, 2020).

Implementation researchers and health economists share an interest in impacting real-world issues and policy, which motivates collaborative research. Different economic theories, methodologies, and applications can further inform decision-making processes and optimize implementation strategies (Beidas et al., 2021). An important unifying, and at the same time distinctive, aspect is related to the emphasis on establishing causality (Angrist & Pischke, 2009, p.221–247; Lewis et al., 2018, p.229–244; Rabin & Brownson, 2012, p.23–51). Where implementation science aims to theoretically explain the causal mechanisms of implementation, such as how healthcare professionals' attitudes and beliefs predict their adherence to clinical guidelines in practice (Lewis et al., 2018, p.229–244; Rabin & Brownson, 2012, p.23–51), health economics have methodological strengths in the empirical research

of causal inference using econometric experiments (i.e. Angrist & Pischke, 2009, p.1–22) presented in Chapter 3.3. Health economists could contribute to implementation research by establishing causality and evaluating the influence of implementation strategies using quasi-experimental study designs and administrative data, while advantaged by the implementation researchers' knowledge of the theoretical and practical understanding of the implementation process (Barnett et al., 2020).

3.2 Economic evaluation of implementation strategies

Advancements in medical technology have been shown to lead to higher costs, as new technologies often come with higher prices and can drive up overall healthcare spending. This finding highlights the need for decision-makers to carefully consider the cost-effectiveness and value of adopting new technologies to ensure sustainable healthcare spending (Chandra & Skinner, 2012). Cost is frequently cited as a major barrier to implementing and sustaining EBPs and decision-makers must intelligently use limited resources to maximize benefits (Fischer et al., 2016; Grol & Grimshaw, 2003; Powell et al., 2019). Therefore, they need to consider the costs and benefits of implementation strategies and the potential outcomes from changing practices (Grimshaw et al., 2004; Hoomans & Severens, 2014). Due to resource constraints, not all implementation strategies can be supported and trade-offs between implementation strategies become necessary (Hoomans & Severens, 2014).

Economic evaluation compares costs to benefits and reveals the opportunity cost of choices, providing a comparative analysis of alternative actions in terms of their costs and consequences (Hoomans & Severens, 2014; Powell et al., 2019). There are generally four types of economic evaluations: cost-benefit analysis, cost-minimization analysis, cost-effectiveness analysis, and cost-utility analysis (Drummond et al., 2015, p. 1–18). Cost-effectiveness and cost-utility analysis can help determine the most efficient implementation strategy by comparing their costs to the

associated health benefits. However, cost-minimization studies are generally insufficient to establish whether an implementation strategy is economically sensible. (Hoomans & Severens, 2014). In cost-effectiveness analysis, the outcome can be any patient outcome, and cost-utility analysis is a more specific form of cost-effectiveness analysis in which health is summarized as a composite measure of mortality and morbidity, most commonly via quality adjusted life years (QALYs) (Drummond et al., 2015, p.1–18).

Decisions are made at different levels of the implementation process by various stakeholders, which are divided into patients, healthcare professionals, and policymakers (Proctor et al. 2011; Lewis et al., 2018, p.229–244). Therefore, there can be different perspectives to consider when conducting economic evaluation of implementation strategies. Depending on the specific service and population, these perspectives may range from the patient and caregiver to healthcare organizations and wider society (Gold et al., 2022; Roberts et al., 2019). Unlike economic evaluations of interventions, it is even recommended to conduct economic evaluations from narrower perspectives related to the particular interests of key stakeholders (Eisman et al., 2021). It is argued that the societal perspective might not be the most useful when it comes to implementation strategies. The perspective of the organizational decision-maker is often the priority because the goal of implementation strategies is to generate pragmatic information that will bridge the gap between research and practice for EBPs (Saldana et al., 2022).

Economic evaluations of implementation strategies are likely to have different outcomes of interest than intervention evaluations. Outcomes for intervention evaluation aim to assess the intervention's health effect at the individual level, and health utility measures such as QALYs are preferred. Instead of health effects, implementation studies often focus on organizational outcomes such as adoption, feasibility, fidelity, penetration, and sustainability (Saldana et al., 2022). Therefore, the cost-effectiveness of implementation strategies also depends critically on the effect they have on healthcare provider and patient behaviour (Hoomans & Severens,

2014). However, this range of potential outcomes brings up significant questions regarding which outcomes will be optimized, the existing limitations, and how these variations might diverge based on different viewpoints (Eisman et al., 2021). Another disadvantage is that the incremental cost-effectiveness ratio (ICER) cannot be compared to results from other studies. In addition, determining a cost-effectiveness threshold ratio is difficult with context-specific outcomes (Eisman et al., 2020).

Compared with economic evaluations of interventions, the range of possible costs and effects associated with implementation strategies is wider (Grimshaw et al., 2004; Hoomans et al., 2007). It is said that intervention costs should be estimated separately from the implementation costs (Gold et al., 2022). Costs typically not included in the economic evaluations of interventions are costs of information delivery, and learning and unlearning, which are important parts of implementation costs. Different types of costs may be incurred in different stages of the implementation process and there has been disagreement in the literature regarding which activities and costs should be counted as part of the implementation process (Gold et al., 2022; Hoomans & Severens, 2014).

According to Hoomans and Severens (2014), the cost of implementation may include the following: "1) costs associated with executing implementation strategies, 2) the excess cost of service delivery as uptake or implementation changes, 3) the opportunity cost to providers and patients partaking in the implementation activities, and 4) research and development-related expenses resulting from the process of implementing change". In addition, it is suggested that implementation analyses should differentiate between fixed and variable costs whenever possible. Economists view fixed and variable costs based on whether they vary with the scale of production, and the costs of an implementation strategy are fixed if they do not change with upscaling (Gold et al., 2022). In addition, less used but still recommended to include in the calculation of implementation costs are sunk costs. Sunk costs can be, for example, costs related to development and the costs of changes in healthcare provision (Hoomans et al., 2007).

The number of economic evaluations and costs of implementation strategies is increasing; however, considerable variation was found among the descriptions and definitions of the heterogeneous and complex strategies (Michaud et al., 2022). Similarly, as outlined in a recent review, randomized trials involving de-implementation rarely provided comprehensive accounts of intervention costs or their effects on healthcare expenditures (Falkenbach et al., 2023). A standardized approach "The Cost of Implementing New Strategies" (COINS) for mapping the costs associated with implementation activities has been introduced. COINS is based on the Stages of Implementation Completion (SIC), a tool that consists of three phases of implementation: pre-implementation, implementation, and sustainability. The SIC has the potential to assess different levels of costs at different points in the implementation process, depending on the implementation strategy used (Saldana et al., 2014). However, further research and adaptation may be necessary to broaden the perspective and account for a wider range of costs in different contexts and practices (Eisman et al., 2021; Gold et al., 2022; Saldana et al., 2022).

The quantity and quality of economic evaluations in implementation research have increased during recent decades. Five literature reviews have been recognized to capture the economic evaluations of implementation strategies (Grimshaw et al., 2004; Hoomans et al., 2007; Reeves et al., 2019; Roberts et al., 2019; Vale et al., 2007). Different methods are used in economic evaluations, but it is suggested that a total net benefit approach and decision analytic modelling should be used more widely (Hoomans et al., 2011; Hoomans & Severens, 2014; Krebs & Nosyk, 2021). Total net benefit is less used in implementation strategy evaluation, although it helps to assess the value of implementation under conditions of uncertainty. The total net benefit of an implementation strategy is a function of its incremental costs and effects in comparison with another strategy or standard care, the duration of strategy's usage or validity, and the size of the patient population served (Hoomans et al. 2011). Decision analytic modelling is an approach for both data synthesis and data extrapolation in economic evaluation. In modelling studies, economic data

may be synthesized from a range of sources rather than from a single trial or observational study (Hoomans & Severens 2014: Hoomans et al., 2007).

Quantitative economic evaluations are essential for investigating the cost-effectiveness of implementation strategies; however, they may have a limited ability to capture the contexts and stakeholders' perspectives. In implementation research, the outcomes and costs are dependent on the context. Therefore, implementation scientists are encouraged to use mixed-methods design in economic evaluations collecting and tracking implementation costs and benefits (Dopp et al., 2019; O'Leary et al., 2022). By incorporating qualitative methods, such as interviews and ethnographic fieldwork, implementation research could enrich economic evaluations with context-specific information that may facilitate richer insights and better understandings of causal relationships in complex settings (Dopp et al., 2019; Salloum et al., 2022). There is a greater risk of continuing sub-optimal implementation strategies if the evaluations are not intentionally conducted. However, the need for additional qualitative analysis within economic evaluation should always be addressed, because it requires resources (O'Leary et al., 2022).

3.3 Evaluation of implementation strategies using quasi-experimental designs

Quasi-experimental studies are conducted where there are practical or ethical barriers to conducting RCTs (Grimshaw et al., 2000). RCTs are considered the most robust method of assessing the effects of healthcare interventions. Randomization minimizes selection bias and maximizes the likelihood that measured and unmeasured confounding variables are distributed equally (Handley et al., 2018). However, when evaluating implementation strategies, patient randomized trials may be less robust because of contamination and RCTs must involve a random assignment of patient groups. In cluster randomized controlled trials (cRCT), groups of participants, such as patients within clinical practices, serve as the unit of

randomization. While clustering minimizes the risk of contamination, it runs into problems with confounding, especially for trials with few sites randomized (Miller et al., 2020). The assumption of RCTs is that the outcome is independent from patients. However, in cRCTs, the patients within a cluster may respond in a similar manner which violates this assumption (Grimshaw et al., 2000).

In real-world settings, such as evaluating the implementation of EBP, any form of random allocation is often not possible due to practical, ethical, social, or logistical constraints. Therefore, quasi-experimental designs are applied when aiming to assess the effects of implementation strategies (Handley et al., 2018). The three most used quasi-experimental designs in implementation evaluation studies are: uncontrolled before and after studies, time series designs, and controlled before and after studies (Grimshaw et al., 2000).

The results of uncontrolled before and after studies may overestimate the effects of interventions; therefore, the results of studies using such designs have to be interpreted with caution (Grimshaw et al., 2000). Controversially, controlled before and after studies are the most robust quasi-experimental method for evaluating effects of implementation strategies. In controlled before and after studies, a control population is identified, and it needs to have similar characteristics and performance to the study population. It is also expected to experience secular trends similar to the study population. In this design, analysis comparing performance in the study and control groups following the implementation is undertaken, and any observed differences are assumed to be due to the implementation of EBP (Grimshaw, 2000). However, it may be challenging to find an appropriate confounder for the lack of information available to determine an equivalent comparison group. One strategy is matched case-control design, which involves matching individuals with similar characteristics, such as demographics, for the control groups. Theoretically, both groups are exposed to the same trends in the environment, making it plausible to determine if implementation had a causal effect (Handley, 2018).

Another more robust way of conducting a controlled before and after study and proving causal inference of an implementation strategy is the Difference-in-Differences (DiD) design, also called a comparative interrupted time series design or a non-equivalent control group pre-test design (Wing et al., 2018). In the DiD design, the change in the untreated group is used to represent all non-treatment changes in the treated group. The method is simple in theory: when the untreated group's change is taken away, it leaves the change in the treated group that represents effectiveness of the implementation strategy. However, the method relies on the assumption of a parallel trend between the groups, which can be investigated using data from pre-intervention periods but is not always observed. If the parallel trend assumption does not hold, another unidentified factor interferes with the difference between the groups, violating causality (Angrist & Pischke, 2009, p.221–247).

When identifying an appropriate control group is impossible, a time series design can be used to detect whether an implementation strategy has an association significantly greater than the underlying trend. Several statistical time series techniques have been used depending on the characteristics of the data. The most important determinant of the method is the number of data points prior to the intervention to provide a stable estimate of the underlying trend (Grimshaw et al., 2000; Handley et al., 2018). Interrupted time series (ITS) design assumes that level and trend in a given outcome measure in the group exposed to the intervention would have remained the same in the absence of the intervention. ITS analysis is considered a robust quasi-experimental design for evaluating healthcare interventions and implementation strategies. The downside of ITS design is that it does not provide protection against the influence of other events occurring at the same time (Grimshaw et al., 2000; Hategeka et al., 2020; Jandoc et al., 2015). In comparison with simple before and after designs, the key advantage of ITS designs is that they look for an interventions' influence while accounting for pre-intervention trends (Miller, 2020; Handley, 2018).

The use of ITS design in the evaluation of healthcare quality improvement interventions, and in health research, has increased considerably over the past decade (Ewusie et al., 2020; Hategeka et al., 2020; Jandoc et al., 2015). Several statistical methods are available for analysing ITS data, and there is significant variation in methodological considerations in ITS analysis (Hategeka et al., 2020; Ewusie et al., 2020). Autocorrelation, seasonality and non-stationarity should be considered in the analysis, which Autoregressive Integrated Moving Average (ARIMA) models inherently account for (Schaffer et al., 2021). However, the most common ITS methods in health research were segmented regression, which poorly reported these issues (Hategeka et al., 2020; Jandoc et al., 2015).

In total, there are different types of quasi-experimental study designs, and it is recommended to always use the most robust statistical analysis available (Grimshaw et al., 2000; Handley et al., 2018). However, the available data, the absence of an equivalent comparison group, or the setting of the implementation strategy itself may limit the possibilities of establishing well-operationalized causal questions, especially retrospectively. Therefore, well designed and planned prospective implementation research is recommended (Barnett et al., 2020, 2021) and the distinction between causation and association should be recognized when interpreting the results of quasi-experimental studies (Hernán, 2004; Haber et al., 2022).

3.4 Physician behaviour and social network influence on implementation of evidence-based practice

The implementation of EBP necessitates changes in the behaviour of stakeholders (Francis et al., 2012). As a result, behaviour change techniques are utilized in implementation strategies to facilitate both implementation and de-implementation (Grimshaw et al., 2002, 2020; Michie et al., 2008). Patients, healthcare professionals, and policymakers

have important roles in the implementation process (Lewis et al., 2018, p.229–244). Stakeholders' behavioural change is influenced by a wide range of factors, such as stakeholders' knowledge, skills and motivation, and the physical and social environment (Wang & Groene, 2020). One way of categorizing individuals is rooted in the Diffusion of Innovations theory, which suggests that the success of implementation is based on stakeholders' readiness for change (Rogers, 2003, p.267–299). According to the theory, innovations are typically adopted in stages — first by innovators, then early adopters, and eventually by laggards over time. The theory highlights the fact that individuals act differently, which may naturally hinder the implementation process (Rogers, 2003, p.267–299).

Physicians are key stakeholders in healthcare, and implementation research and health economics have been more focused on physicians' behaviour change within organizational constraints as a key target to improving the quality of care and guideline adherence (Miraldo et al., 2019: Grimshaw et al., 2002; Grol & Grimshaw, 2003). Implementation researchers have noted the need to conceptualize physician behaviour change and explore the applicability of behavioural theories to the understanding of professional behaviour change (Grimshaw et al., 2002). An overview of systematic reviews by Johnson and May (2015) demonstrated that various types of education may change professional behaviour. In addition, social environment and peer group behaviour were found to be important factors influencing behaviour change in healthcare professionals. This may be because, in a complex environment, EBP is implemented through collective action, which takes place when people work together and legitimize new knowledge and practice norms through experience (Johnson & May, 2015).

Physicians' socio-demographic characteristics, experience, workload, enthusiasm, specialty and uncertainty over the best practice correlated with practice style in the adoption of innovations across different medical specialties (Miraldo et al., 2019). Moreover, the Diffusion of Innovations theory suggests that the diffusion of innovation spreads through social networks and social structure influences diffusion through values, norms,

roles, and hierarchies. Stakeholders exchange information and interact within these networks, and the adoption of innovations is more likely if peers share a positive evaluation of the innovation. Individuals within a social network often serve as sources of information on innovations as they participate in multiple networks simultaneously (Rogers, 2003, p.300–365).

This peer effect is a part of social learning, which is the process of information transmission between individuals. The effect can be detected by changes in an individual's behaviour in response to that of their peers. The role of physicians' social network (i.e., peers in the same practice or hospital, patient-sharing peers or medical student groups) and its relation to service provision and patient outcomes have been studied in different healthcare settings (e.g., Avdic et al., 2023; Chambers et al., 2012). Physicians' incentives and incorporation of behavioural economic principles, such as peer-comparison, have the potential to make healthcare more effective (Emanuel et al., 2016; Navathe et al., 2020).

Social network analysis (SNA) is an approach to examining social relationships and is well suited for examining implementation research questions related to the social structure of service settings, key actors, how social relationships change, and explanations of implementation outcomes (Bunger & Nooraie, 2020, p.487–496). SNA has been used to map the connections between physicians and identify social contagion, which describes the influence of the opinion of colleagues about an innovation on the adoption decision (Van den Bulte & Lilien, 2001). Coleman et al. (1957; 1959) were the first to study the diffusion of innovation among physicians and found that physicians' social relations accelerated the adoption of a new drug. SNA has shown that physicians in different collaborative arrangements have a similar prescribing behaviour (Fattore et al., 2009) and regional variation may be due to social norms within physicians' medical communities (Keating et al., 2007, 2020).

SNA is traditionally conducted using physicians' self-reported connections, but in recent years, administrative data has been used more widely to identify peer relationships between physicians. Several ways to

identify peers have been developed, and one of them is patient-sharing where two physicians are considered to be connected to one another if they both deliver care to the same patient (DuGoff et al., 2018). Theoretically, physicians sharing patients are expected to have contact, which increases the likelihood of integrated practice styles (Donohue et al., 2018; DuGoff et al., 2018). Barnett et al. (2011) reported that patient-sharing, as measured using administrative patient data to identify connections between physicians, is a valid method for identifying physician networks.

Recent findings suggest that peer networks have a positive influence on the diffusion of new medicines. Medical innovations are more likely to be adopted if peers share their positive evaluation of the new treatment (DuGoff et al., 2018). Peer physicians may increase the adoption of new medicines as they engage in discussions about new practice styles and learn from each other (Agha & Zeltzer, 2022; Donohue et al., 2018; Yang et al., 2014). However, there is relatively little research on physician practice variation and peer effect related to the de-implementation of low-value prescribing (Sacarny et al., 2019). It has also been suggested that the de-implementation of low-value care, in particular, may be influenced by other physicians and the social environment (Ingvarsson et al., 2020; Patey et al., 2021).

4 Dementia care and potentially inappropriate medications

4.1 Dementia care in Finland

Dementia, also referred to as memory or cognitive disorder, is a syndrome in which there is many forms of disturbance in memory underlining cognitive functions, including thinking, orientation, comprehension, calculation, learning capacity, language, and judgement (Livingston et al., 2017). Dementia decreases the well-being of people living with it and the ability to perform everyday activities, and is one of the main reasons for long-term inpatient care (Burley et al., 2020). Dementia incidence increases with older age, and is a major cause of disability in later life. Alzheimer's disease is the most common form of dementia, accounting for 60-70% of cases, but there are many other forms, such as vascular dementia and dementia with Lewy bodies (Livingston et al., 2017). No cure is currently available for dementia; however, there is much that can be done to improve the lives of people with dementia and their caregivers (Livingston et al., 2017). The first-line treatment for dementia is anti-dementia medication, which can slow down its progression (Current Care Guidelines, 2017) and delay admission to institutionalized care (Halminen et al., 2021).

Dementia is a major global health issue as it affects around 55 million people worldwide. Its global cost is 1.3 trillion US$ (0,8% of GDP) and its prevalence is expected to increase in the near future (World Health Organization, 2021). Finland is one of the most rapidly aging countries, and older people more often live with dementia. There are approximately 190,000 people with dementia and 14,500 new cases each year (Finnish Institute for Health and Welfare, 2023). In 2020, there were 105,683 community-dwelling Finns aged over 65 years who used anti-dementia medication (Rantsi et al., 2023) and there are people living with

undiagnosed dementia or with dementia diagnoses but not taking anti-dementia medication (Vesikansa et al., 2022).

To optimize dementia care, the Finnish Medical Society Duodecim has published clinical guidelines (Current Care Guidelines) for memory disorders. The Finnish Current Care guidelines are formed from a systematic review of evidence, and they serve as support for the treatment decisions of healthcare professionals. The Finnish Current Care Guidelines on Memory Disorders were originally published in 2006 and outlined the Guidelines to Diagnose Alzheimer's disease. The guidelines were updated in 2010 to include other forms of dementia. Eventually, the guidelines were again updated in January 2017, after which they included guidance on the treatment of BPSD (Current Care Guidelines, 2017). The guidelines recommend personalized care plans in dementia care. A personalized care plan includes strategies engaging stakeholders in person-centred care and approaches tailored to care givers, as well as integrating behavioural and environmental approaches into dementia care (Kales et al., 2015, 2019; Current Care Guidelines, 2017).

Dementia care in Finland is organized by local authorities and funded by taxation, the NHI scheme, and user fees (Linnosmaa & Nguyen, 2016). The average annual costs of care are estimated to be 16,448€ per person with early Alzheimer's disease. A significant association with increased costs was detected in the transition from early to mild Alzheimer's disease (29,053€), and further to severe Alzheimer's disease (56,252€). (Jetsonen et al., 2021). Most older people with dementia in Finland are community-dwelling, which means that they may live independently, receive informal care, use home-care services or reside in assisted living facilities. Over 20% of clients in home care and over 50% of clients in sheltered housing units with 24-hour assistance were living with dementia in 2015 (Finnish Institute for Health and Welfare, 2017, A&B). Some of the assisted living facilities are sheltered housing units with 24-hour assistance. Care in these homelike environments is comparable to nursing homes, but unlike inpatient care (nursing homes and hospital wards) assisted living facilities are part of community care (Linnosmaa & Nguyen, 2016).

Long-term inpatient care considerably decreased during the 2000s in Finland, and at the same time, the share of sheltered housing units with 24-hour assistance increased due to different funding allocation mechanisms (Mielikäinen & Kuronen, 2022). The change in service systems is presented in Figure 2. Consequently, every year, there are a higher proportion of frail community-dwelling older people. One difference between 24-hour assistance housing and inpatient care is that community-dwelling residents' prescription medicine purchases are reimbursed by the NHI scheme in assisted living facilities, whereas in long-term inpatient care, medicines are covered by the care units (Linnosmaa & Nguyen, 2016).

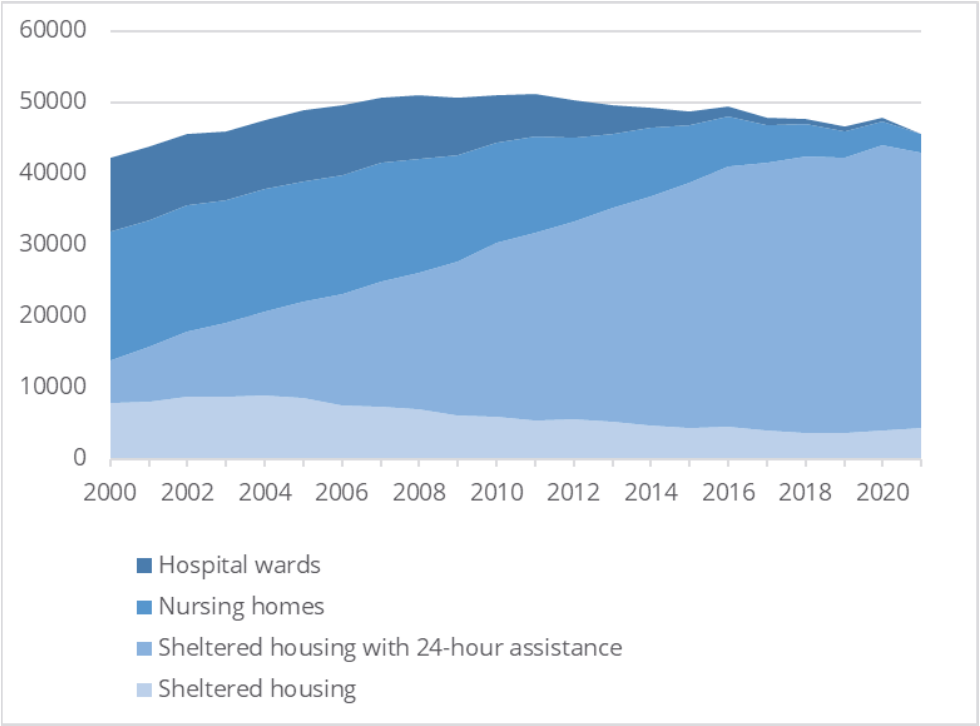

Figure 2. Older population in housing services and inpatient care in Finland (Mielikäinen & Kuronen, 2022).

In 2012, the Finnish Ministry of Social Affairs and Health produced a National Memory Programme to create a "memory-friendly" Finland. One of the main objectives of the programme was to ensure a good quality of life for people with dementia and their families through timely support, treatment, rehabilitation, and services. Since 2012, local authorities have been responsible for setting up regional outpatient clinics offering primary healthcare services to people with dementia. In 2014, Finland had 152 local authorities (municipalities or municipal federations) responsible for organizing primary healthcare and services, including support for people with dementia and their families. In addition, there were 22 hospital districts in Finland (and 5 university hospital districts) responsible for offering specialist medical care to people with dementia and to provide primary healthcare consultation and training (Finnish Ministry of Social Affairs and Health, 2013).[1]

The Alzheimer Society of Finland conducts a Memory Barometer survey for monitoring the implementation of the National Memory Programme and local authorities' developmental needs. This takes place every five years and 86% of the participating local authorities had regional outpatient dementia clinics and 3% had no clinic or even a memory nurse in 2020 (response rate 79%). In addition, 84% of the participating local authorities reported to have person-centred care pathways as a practice (Tommola et al., 2020). A study by Tolppanen et al. (2015) found only small regional variation in healthcare service use and costs of people with Alzheimer's disease. They found some indication that regions with higher inpatient admissions to general healthcare had lower inpatient admissions to specialized care (Tolppanen et al., 2015).

[1] In early 2023, a major reform of social and healthcare was implemented and currently the Finnish healthcare system is not as decentralized. Under the reform, a total of 21 self-governing wellbeing services counties were established. The wellbeing services counties and the City of Helsinki are responsible for organising health, social and rescue services within their areas. (Finnish Ministry of Social Affairs and Health, 2023).

4.2 Evidence-based treatment of behavioural and psychological symptoms of dementia

Up to 90% of people with dementia develop BPSD, also referred to as NPS, during their illness. BPSD is a broad term for neuropsychiatric symptoms including mood disorders, depression, agitation, psychosis, sleep disturbances, anxiety, apathy, dysphoria, aberrant motor activity, hallucinations, and delusions (Ballard et al., 2008; Finkel et al., 1996; Lyketsos et al., 2000; Phan et al., 2019). Transparently, BPSD decreases the well-being of people with dementia and causes stress for caregivers (Ballard et al., 2008; Howard et al., 2001). BPSD are a main predictor for long-term care (Cepoiu-Martin et al., 2016) and institutionalization (Toot et al., 2017), and a notable reason for the social and economic costs of dementia (Burley et al., 2020).

Psychotropic medication is prevalent in the treatment of BPSD, although older people with dementia are more prone to side effects and their use of psychotropics has been associated with potential harms including falls, fractures, and mortality (e.g., Byerly et al., 2001; Maust et al., 2015; Saarelainen et al., 2017; Schneider et al., 2005; Watt et al., 2021). Medication use in the older population in general can be classified as potentially inappropriate if the associated risks outweigh the potential benefits and PIM use should be avoided among older people (Renom-Guiteras et al., 2015). PIM use is associated with adverse drug events, reduced cognitive and physical functioning, increased falls, hospitalization, and mortality (e.g., Berdot et al., 2009; Hyttinen et al., 2016; Xing et al., 2019). According to recent meta-analysis, PIM use is prevalent in older people with dementia (pooled estimate 43%), but it varies widely (Zhao et al., 2023).

Psychotropics are defined as potentially inappropriate in people with dementia, also referred to as low-value psychotropics (Platen et al., 2021, 2022). Especially antipsychotics have been associated with increased mortality, among other adverse events (Gill et al., 2007; Schneider et al., 2005). On the other hand, non-pharmacological interventions, such as

individualized care, caregiver training, modifying environmental factors, individualized therapy, exercise, music therapy, or massaging, have been shown to have a similar effect size to psychotropic medications. Non-pharmacological interventions have a lower risk of potential harms and they are potentially cost-effective compared to psychotropic treatments (Azermai et al., 2012; Nickel et al., 2018; Watt et al., 2021). In addition, people with dementia experienced non-pharmacological interventions as meaningful and strengthening their self-esteem (Tuomikoski et al., 2022).

According to the Finnish Current Care Guidelines, among other clinical guidelines the first-line pharmacological treatment for dementia and BPSD is anti-dementia medication. In addition to the onset of anti-dementia medication non-pharmacological interventions are recommended as a primary treatment of BPSD, and the initiation of psychotropics, especially antiepileptics and antipsychotics, is recommended to be avoided; their initiation is recommended only in cases of non-pharmacological interventions failing (Current Care Guidelines, 2017). If necessary, psychotropics should only be used in the short-term and it is recommended to evaluate their necessity every 3−6 months (Current Care Guidelines, 2017; Azermai et al., 2012).

Physicians have a legal and ethical obligation to treat patients in accordance with good medical practice in agreement with the patient. The Finnish Current Care Guidelines are recommendations for the best practice, and eventually physicians may perform generally accepted and justified procedures in accordance with their training (Current Care Guidelines, 2017). Physicians making the decision about medications and the short-term use of psychotropics in the treatment of BPSD is reasonable in some acute situations, e.g., where stakeholder safety may be at risk (Kales et al., 2019). In any case, the decision about the treatment and its rationale should be noted in medical records (Act on the Status and Right of Patients 17 §).

In addition to clinical guidelines, Choosing Wisely, an international initiative to reduce ineffective or harmful healthcare, recommend avoiding antipsychotics in people with dementia. The Choosing Wisely initiative was

Introduced in 2012 with the aim of facilitating conversations between physicians and patients, encouraging them to consider alternatives to low-value care (American Geriatric Society, 2015). The Finnish Choosing Wisely published their recommendations considering antipsychotics prescriptions in 2018. These were produced from existing evidence-based guidelines where evidence-based medicine methods and processes ensure high quality (Sipilä et al., 2019).

In addition, several criteria to reduce PIMs in older people in general have been developed, e.g., the Beers criteria (Beers et al., 1991) from the United States and, from Europe, the Laroche criteria (Laroche et al., 2007) and the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions and Screening Tool to Alert to Right Treatment (STOPP/START) (O'Mahony et al., 2015). In addition, PIM criteria have been nationally published in many countries, including the Meds75+ database in Finland, which is updated every year and was originally published in 2010 (Finnish Medical Agency, 2023).

Despite publications and updates to clinical guidelines on dementia and PIM criteria in Finland (The Finnish Current Care Guidelines on Memory Disorders in 2017, Choosing Wisely in 2018, Meds75+ in 2010), their implementation and influence on PIM prescribing was not investigated before the MEDIFF project. Although implementation and dissemination research in dementia care is plentiful, financial strategies are rare, as well as the evaluations of implementation sustainability and evaluations using patient level outcomes (Lourida et al., 2017).

4.3 Prevalence of and factors associated with psychotropic use among older people with dementia

Rates of psychotropics, especially antipsychotics, in older people with dementia is widely studied, and the prevalence has been high (Guthrie et al., 2010; Jester et al., 2021; Martinez et al., 2013; Maust et al., 2020;

Nørgaard et al., 2017). A recent meta-analysis estimated that 33% of nursing home residents received two or more psychotropics (Jester et al., 2021). Based on a meta-analysis by Kirkham et al. (2017), the pooled prevalence of antipsychotic use among people with dementia was 27.5%. Subgroup analyses showed that community settings had a lower prevalence of antipsychotic use (12.3%) compared with long-term inpatient care (37.5%). Likewise, in Finland, the prevalence of psychotropics in people living in long-term inpatient care (nursing homes and 24-hour assistance housing) has been higher (over 60%) than in community-dwelling people, although the prevalence in long-term inpatient care decreased from 2003 to 2017 (Roitto et al., 2019).

In 2005–2011, of community-dwelling people diagnosed with Alzheimer's disease, 53% purchased at least one psychotropic and 20% purchased antipsychotics. People with Alzheimer's disease were six times more likely to use antipsychotics and three times more likely to use antidepressants compared to without Alzheimer's disease (Taipale et al., 2014). Over this six-year period, 18% of people with Alzheimer's disease used concomitantly two or more psychotropics (Orsel et al., 2018). Further, 52% of Finnish community-dwelling people with dementia purchased at least one psychotropic in 2020 (Rantsi et al., 2023). Most psychotropics for community-dwelling people with Alzheimer's disease were prescribed by non-specialized physicians (48–60% of the first prescriptions of psychotropic drug classes). The specialized physicians prescribing to people with Alzheimer's disease were geriatricians, neurologists and psychiatrists (Taipale et al., 2014).

Psychotropic use in people with dementia is associated with higher age and multimorbidity (Brett et al., 2018). According to Orsel et al. (2018), patient-related factors associated with psychotropic use among persons with Alzheimer's disease in Finland were female gender, asthma/chronic obstructive pulmonary disease, hip fracture, stroke, history of psychiatric disorder, and any cardiovascular disease. Three years before Alzheimer's diagnosis, participants were more likely to use psychotropics when aged

over 85 years. In contrast, three years after diagnosis, persons aged under 65 years were more likely to use psychotropics (Orsel et al., 2018).

In addition to factors related to patients, healthcare organizations and professionals may also influence treatment choice. Some studies from Finland have found regional variation related to dementia care and PIM prescribing. Regional variation between university hospitals was estimated in the use of any psychotropic and antipsychotics in people with dementia, but this diminished between 2005 and 2011 (Tolppanen et al., 2017). Hyttinen et al. (2017) found that overall, PIM initiation in older people depended on both patient characteristics and healthcare practices between university hospital districts. In a recent study by Paulamäki et al. (2023), PIM prevalence was found to vary between hospital districts. The higher prevalence of PIMs was suggested to be related to a shortage of physicians in primary healthcare, a higher share of older people with excessive polypharmacy, and a lower share of home care personnel. A greater share of people with dementia was not associated with higher PIM prevalence (Paulamäki et al., 2023).

Multidisciplinary healthcare staff play a key role in providing non-pharmacological interventions in the treatment of BPSD, while physicians make the decision to prescribe psychotropics (Kales et al., 2015). Dementia care can be challenging, and prescribing practice and factors associated with prescribing have been studied in recent years. Physicians have experienced that insufficient primary care resources, justification, and the role of families are factors associated with psychotropics prescribing (Jennings et al., 2018). Physicians generally expressed awareness and agreement with current clinical guidelines for psychotropics use, but some physicians also criticized the regulation of psychotropics prescribing as potentially not improving care (Bednarczyk et al., 2022). According to Turner et al. (2004), physicians' knowledge of dementia diagnosis and management was good, but two-thirds lacked confidence in the management of BPSD. Physicians may find managing dementia stressful, and the benefits of antipsychotics were sometimes over-estimated and potential harmful side-effects overlooked (Jennings et al., 2018; Kales et al.,

2015). Based on previous studies, the main barriers to implementing non-pharmacological interventions were low levels of staffing and resourcing issues to conduct time consuming non-pharmacological interventions (Dhuny et al., 2021; Wood-Mitchell et al., 2008). However, the generalizability of these findings is limited due to qualitative approaches and small sample sizes.

4.4 Implementation strategies to reduce potentially inappropriate medication use

Several implementation strategies to facilitate the implementation of reducing PIM use in older people have been conducted and their effectiveness has been comprehensively studied. These implementation strategies are usually categorized into medication reviews, multidisciplinary interventions, computerized systems, educational interventions, and other interventions (Santos et al., 2019). Implementation strategies, either alone or combined, may reduce the use of PIMs in different settings, especially in the short-term. Although, the economic impact or the health benefits of reducing PIM prescribing is not well known (Alldred et al., 2016; Clyne et al., 2012; Santos et al., 2019).

A medication review is an exhaustive evaluation and discussion of a patient's medications performed by a pharmacist or a physician. Medication reviews with a clinical pharmacist may have a positive influence on the use of medicines, but no positive effect was found on hospital admissions and mortality, especially in nursing homes (Santos et al., 2019; Wallerstedt et al., 2014). However, the cost-effectiveness of medication reviews is uncertain and the clinical benefits are not well known (Loganathan et al., 2011; O'Connor et al., 2012; Topinková et al., 2012). Acceptance by physicians is an important parameter when a medication review is performed by a pharmacist, but this was not mentioned in most of the studies (Santos et al., 2019).

Multidisciplinary intervention refers to a quality improvement initiative where the clinical practice of pharmacists is integrated with a multidisciplinary team (physicians, nurses and other members of the healthcare team) as part of the care process. Multidisciplinary interventions seem to improve the prescriptions of older patients, but no evidence for reducing adverse events and admissions was found (Loganathan et al., 2011; O'Connor et al., 2012; Santos et al., 2019). Multidisciplinary interventions based on audit and feedback improved PIM prescribing according to Kaur et al. (2009). However, they can be time consuming and resource intensive, and they have mostly been available to hospital services (O'Connor et al., 2012).

Computerized systems are designed to support healthcare professionals when prescribing, and there are some findings that support their ability to reduce PIM prescribing (Clyne et al., 2012; Santos et al., 2019; Topinková et al., 2012). However, they may be costly and logistically difficult interventions to implement on a large scale (O'Connor et al., 2012). Loganathan et al. (2011) did not find a significant difference in PIM prescribing in nursing homes after the implementation of a computerized clinical decision support system. It was suggested that the lack of effectiveness could be attributed to a high number of alerts in the system, and more research is needed (Loganathan et al., 2011).

Educational interventions include educational sessions, distribution of educational materials, and training for different stakeholders. They are found to reduce PIM prescribing and hospitalization periods (Santos et al., 2019; Loganathan et al., 2011). However, interactive approaches with direct feedback appeared to be more effective than passive dissemination of guidelines or written material (Kaur et al., 2009; O'Connor et al., 2012). Educational interventions that successfully reduced PIM prescribing included face-to-face academic detailing, interaction between the prescriber and a group of specialists, and workshops for nurses. On the other hand, interventions with fewer educational sessions and poor participant attendance did not show significant improvement in PIM prescribing (Loganathan et al. 2011).

Other interventions to reduce the number of prescriptions of PIMs for older patients include, for example, clinical guidelines, geriatric medicine services and regulatory interventions. Clinical guidelines are used to reduce variation in healthcare provision and prevent PIM prescribing, but the effectiveness of their dissemination has not been widely assessed (Santos et al., 2019). There are some recent studies on the implementation of clinical dementia guidelines. These ITS analyses found some changes in trends of psychotropic use among older people with dementia in nursing home environments (Gallini et al., 2014; Gerlach et al., 2021; Maust et al., 2018; Valiyeva et al., 2008). The findings suggest slowed growth in atypical antipsychotics use (Valiyeva et al., 2008) and reduced antipsychotic use in people with dementia in nursing homes and long-term care (Gallini et al., 2014; Gerlach et al., 2021; Maust et al., 2018) following different guidelines and quality improvement initiatives.

Previous studies have focused on the ability of implementation strategies to reduce PIM use, with limited evidence of their effect on health outcomes such as mortality or quality of life (Alldred et al., 2016; Santos et al., 2019). The majority of the effectiveness studies were cRCTs, which is appropriate given the complex nature of implementation strategies, but also increases the risk of bias due to difficulties in accounting for confounding (Alldred et al., 2016). Additionally, the heterogeneity in study design, healthcare settings, divergent outcome measures, and varying study quality present obstacles to drawing conclusive evidence on the effectiveness of implementation strategies (Clyne et al., 2012, Santos et al., 2019, Alldred et al., 2016).

Economic evaluations of implementation strategies to reduce PIM use are rare despite the number of effectiveness studies. Some economic evaluation studies have been conducted on medication reviews (Gallagher et al., 2016; Malet-Larrea et al., 2017), multidisciplinary interventions (Gillespie et al., 2017; Patterson et al., 2011) and educational interventions (Ballard et al., 2018; Sanyal et al., 2020). The educational interventions by Sanyal (2020) and Ballard (2018) were estimated as less costly and more effective than usual care. The studies on medication reviews and

multidisciplinary interventions noted that the decision concerning cost-effectiveness was dependent on the decision makers' valuation of the specific outcome unit. The studies generally evaluated short-term cost-effectiveness and used different outcome measures but the impact on the measured QALYs received less attention.

5 Aims and research questions

The aim of this dissertation was to evaluate implementation strategies for reducing PIM use in older people with dementia using economic evaluation and quasi-experimental study designs. This dissertation consists of three published scientific Articles (I, II, III) and one manuscript (Article IV). The first Article was a scoping review of literature in the field of implementation evaluation on reducing PIM use in older people. The implementation strategies evaluated were an educational intervention (Article II) and the publication of The Finnish Current Care Guidelines on Memory Disorders (Articles III–IV).

Research questions in this dissertation were:

1) How have implementation strategies for reducing PIM prescribing in older people been studied and what are the current knowledge gaps? (Article I)

2) What is the cost-effectiveness of an educational intervention for nurses to reduce PIM use and its impact on QALYs in residents in assisted living facilities compared to treatment as usual? (Article II)

3) What is the relationship between the publication of Finnish Current Care Guidelines on Memory Disorders and the trend of psychotropic use in older community-dwelling people with dementia? (Article III)

4) What is the influence of physician peer network and the Finnish Current Care Guidelines on Memory Disorders on physicians' psychotropic prescribing practice (Article IV)?

6 Data and methods

6.1 Data sources

There were three different data sources used in this dissertation. In Article I, the data consisted of previous studies on the evaluation of implementation strategies for reducing PIMs in older people. The data for Article II was collected during the evaluation of the educational intervention's effectiveness, cRCT, in the years 2011–2012 (Pitkälä et al., 2014). For Articles III and IV, the data was gathered from the Prescription Register maintained by the Social Insurance Institution (SII) of Finland and linked to data from two nationwide registers: 1) the Care Register for Health Care (HILMO) maintained by the Finnish Institute for Health and Welfare (THL) and 2) the registers of causes of death maintained by Statistics Finland (SF). We used the same Prescription Register data in Articles III and IV but in Article III, we used it on the patient level, and in Article IV on the physician level.

Scoping review of implementation strategies for reducing PIM prescribing in older people

In the scoping review (Article I), we searched scientific articles published in English from three appropriate databases: Scopus, Web of Science and PubMed. The search was conducted in November 2019, and we searched for publications after January 2000. Keywords for the search were based on the research question and they were synonyms for the terms older people AND medication AND inappropriate AND implementation. Information specialist Maarit Putous from the University of Eastern Finland provided advice for the search strategy and selecting the databases. See Article I, Appendix A for the detailed search strategy.

Cost-effectiveness analysis of an educational intervention

The data for the cost-effectiveness analysis of an educational intervention (Article II) was collected in years 2011–2012 in assisted living facilities in Helsinki, Finland by the research group of Kaisu Pitkälä at the University of Helsinki (Pitkälä et al., 2014). The follow-up time of the study was 12 months. In total, 20 wards of 36 assisted living facility wards were selected for participation in the cRCT. The Minimum Data Set (Morris et al., 2000) was used to determine the case-mix of each ward. Twenty wards were paired into 10 dyads according to their case-mix. These dyads were randomized to intervention and control groups during 2011 and 2012. Dyads were randomized using a computerized random number generator. We supplemented the original data of cost information in 2020 for the cost-effectiveness analysis.

Registry-based patient and physician level studies

Articles III and IV were registry-based studies. We used the Finnish Prescription Register from the years 2009–2020 (Article III) and 2014–2020 (Article IV). The register maintained by the SII of Finland includes all prescription medication purchases of community-dwelling people receiving reimbursements. All residents in Finland are covered by NHI (Finnish statistics on medicines, 2020). Medication purchases in the Prescription Register are classified based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization, 2018).

The Prescription Register data was linked to inpatient care (≥90 days in hospital ward) from the Care Registers for Social and Health Care (Finnish Institute for Health and Welfare) and causes of deaths (Statistics Finland). In Finland, medications are included in long-term inpatient care and are not reimbursed by the SII (Finnish statistics on medicines, 2020).

6.2 Study populations

Altogether, this dissertation focused on older people with dementia; however, the populations examined in the Articles were somewhat different. In Article I, the perspective was slightly broader than this dissertation overall. To get a wider understanding of the implementation research related to PIM use in older people and fulfil the aim of the MEDIFF project, we also included studies not solely focused on the dementia population in the scoping review.

Articles II–IV focused on the dementia population. In Article II, the participants were residents of assisted living facilities, and 93% of them were diagnosed with dementia, even though admission was not restricted to residents with dementia. In Article III, we included all community-dwelling Finnish people over 65 years who were on anti-dementia medication. In Article IV, we used the same inclusion criteria for medication users as in Article III, but the study population consisted of the physicians who wrote the prescriptions.

Scoping review of evaluations of implementation strategies for reducing PIM prescribing in older people

For the purpose of Article I, we stated that the focus of the included articles was on the evaluation of implementation strategies for reducing PIM use in older people. We used the PCC (Population/Concept/Context) framework to construct meaningful objectives and eligibility criteria in the scoping review (Pollock et al., 2023). The PCC framework used for the scoping review based on the research question is presented in Table 2.

The included studies for the scoping review had the following criteria: 1) patients aged ≥65 years, 2) PIMs defined by validated criteria, 3) decision support for healthcare professionals, 4) implementation process evaluated, 5) original articles and reviews, and 6) quantitative or qualitative methods. We excluded publications where the rational use of medication was mentioned in the context of other purposes (e.g., adherence, timing,

delivery, polypharmacy, no PIM criteria). As the focus of the scoping review was on implementation strategies for healthcare professionals, we excluded publications where the intervention was based on patient education.

Table 2. PPC (Population/Concept/Context) framework

PCC	**How have implementation strategies for reducing PIM prescribing in older people been studied and what are the current knowledge gaps?**
Population	Patients aged ≥65 years
Concept	Implementation process evaluation
Context	Implementation strategies - aimed at healthcare professionals - for reducing PIMs defined by validated criteria

Two authors (Mervi Rantsi & Virva Hyttinen) screened the data independently according to the inclusion criteria in two steps. We discussed the challenges and uncertainties related to the study selection. In addition, in cases of uncertainty, a third opinion from Johanna Jyrkkä was sought. Characteristics of the included publications are presented in detail in Article I, Table 3.

Cost-effectiveness analysis of an educational intervention

In the cost-effectiveness analysis (Article II), the nurses at the intervention wards were the implementation recipients but the residents of the wards were the study population whose well-being was targeted for improvement with the educational intervention. The implementation strategy in this study was an educational intervention consisting of two 4-hour training sessions. Training sessions were based on constructive learning theory and

organized by the research geriatrician. The training sessions aimed to enable nurses to recognize PIMs and adverse drug events. PIMs discussed in the training sessions were the following: Beers Criteria medications (Beers et al., 1991), anticholinergic medications, use of multiple psychotropic medications, Non-steroidal anti-inflammatory drug (NSAIDs), and proton pump inhibitors. The training targeted 2–3 nurses who were responsible for residents' medications in the intervention wards. In seven wards, these nurses participated in both sessions, while in two wards, they missed the first session but participated in the second. In one ward, the nurses did not attend either of the sessions and received tailored individual training. In addition, one geriatrician and one primary care physician participated in one session and received tailored individual training. A more detailed description of the training sessions is presented in Article II.

The participating residents were recruited by nurses, who were not aware which of the wards were randomized to the intervention and control groups. The residents were included if they were aged over 65, living permanently in the assisted living facilities, Finnish speaking, using at least one medication, life expectancy >6 months and able to provide written informed consent (or had a proxy who was able to). Of the 307 eligible residents, 227 participated; 118 residents in the intervention group and 109 in the control group. Characteristics of the participants are presented in Table 3. The mean age of the participants was 83, and 93% were diagnosed with dementia. At the baseline, the residents in the intervention group had a higher number of comorbidities and lower health-related quality of life (HRQoL), measured by the 15-dimensional instrument (15D), than those in the control group. The percentage of females in the intervention group was lower than in the control group and the proportion of participants using PIMs was higher in the intervention group.

Table 3. Characteristics of the study population in the cost-effectiveness analysis

	Intervention group (n=118)	**Control group (n=109)**	**p-value**
Females, n (%)	77 (65.3)	84 (77.1)	0.050
Mean age, years (SD)	82.9 (7.5)	83.5 (6.9)	0.41
CCI, mean (SD)	3.2 (2.0)	2.5 (1.8)	0.004
MMSE, mean (SD)	8.8 (8.2)	10.0 (8.2)	0.25
15D score, mean (SD)	0.61 (0.12)	0.66 (0.11)	0.002
Number of drugs used regularly, mean (SD)	7.5 (2.8)	7.8 (3.1)	0.79
Proportion using PIM, %	83.1	71.6	0.038
Mean number of PIM (SD)	2.9 (1.8)	2.5 (1.7)	0.28
Mean number of psychotropics (SD)	1.13 (.99)	1.34 (.99)	0.11

Abbreviations: SD, standard deviation; CCI, Charlson comorbidity index; MMSE, Mini-Mental State Examination; 15D, 15-dimensional instrument of health-related quality of life; PIM, potentially inappropriate medications.

Registry-based patient level study

The study population of Article III included community-dwelling people aged ≥65 years with anti-dementia medication (ATC-class N06D) purchases (n = 217,778) during the years 2009–2020. People with dementia diagnoses not on anti-dementia medication were not included because the Prescription Register does not contain information about the populations' diagnoses. We divided the study period from January 2009 to December 2020 into 144 observation months. We created a cohort of people with anti-dementia medication, alive, and not in long-term inpatient care for each observation month (1st day). Therefore, the drop-off caused by long-term inpatient care, in addition to mortality, was distinguished from deprescribing. To arrange the cohorts, we defined inpatient care periods as ≥90 days because this is the limit of long-term inpatient care (Finnish statistics on medicines, 2020). We defined the length of each inpatient care period by the individual's check-out date or the next medicine purchase.

The yearly numbers of people using anti-dementia medication and any psychotropics are presented in Table 4.

Table 4. Characteristics of community dwelling older people with anti-dementia medication during the years 2009–2020.

	Older people with dementia[1]			**Older people with dementia using any psychotropics[2]**		
	Total (n)	Female (n, %)	Age, years (mean, SD)	Total (n, %)	Female (n, %)	Age, years (mean, SD)
2009	43,750	29,354 (67.1)	81.7 (6.1)	25,024 (57.2)	17,576 (70.2)	81.8 (6.1)
2010	48,440	32,463 (67.0)	82.0 (6.2)	27,616 (57.0)	19,404 (70.3)	82.1 (6.2)
2011	53,446	35,677 (66.8)	82.3 (6.3)	30,160 (56.4)	21,028 (69.7)	82.4 (6.3)
2012	64,871	43,013 (66.3)	82.4 (6.4)	35,745 (55.1)	24,832 (69.5)	82.5 (6.4)
2013	72,818	48,000 (65.9)	82.6 (6.5)	39,065 (53.6)	27,050 (69.2)	82.7 (6.5)
2014	81,025	52,993 (65.4)	82.8 (6.6)	43,140 (53.2)	29,587 (68.6)	82.9 (6.6)
2015	87,384	56,761 (65.0)	83.0 (6.7)	45,718 (52.3)	31,243 (68.3)	83.1 (6.7)
2016	93,162	60,237 (64.7)	83.1 (6.8)	48,049 (51.6)	32,661 (68.0)	83.3 (6.8)
2017	97,688	63,004 (64.5)	83.2 (6.9)	49,847 (51.0)	33,662 (67.5)	83.3 (6.9)
2018	101,650	65,203 (64.1)	83.3 (6.9)	51,907 (51.1)	34,833 (67.1)	83.4 (6.9)
2019	104,020	66,270 (63.7)	83.3 (7.0)	52,658 (50.6)	35,177 (66.8)	83.5 (7.0)
2020	105,683	66,932 (63.3)	83.4 (7.0)	54,488 (51.6)	36,126 (66.3)	83.5 (7.0)

Abbreviations: SD, standard deviation

[1] Anti-dementia medicine (ATC-N06D) users

[2] Antipsychotics (ATC-N05A), Antidepressants (ATC-N06A), Anxiolytics (ATC-N05B), Hypnotics (ATC-N05C) and Antiepileptics (N03AF02, N03AG01, N03AX16)

Registry-based physician level study

In Article IV, we analysed the influence of physician peer network and the Finnish Current Care Guidelines on Memory Disorders on the prescription of psychotropics on a physician-year level during the years 2014–2020, and the sample was created using physician-anonymized identification numbers (physician IDs). The data included 38,420 physician IDs who prescribed medicine to people over 65 years during the study period. We

followed physicians (n=25,533) who prescribed any medication to ≥1 community-dwelling people on anti-dementia medication (ATC-N06D) not on psychotropic medication 12 months prior to the date of interest (n=164,673). The characteristics of the study population are presented in Table 5.

Table 5. Characteristics of the physicians who prescribed any medication to ≥1 dementia patient during the years 2014–2020.

Physicians (n)	**25,533**
Physicians who prescribed zero psychotropics (n, %)	12,984 (51.0)
Prescribing practice	
Mean number of dementia patients[1] (SD)	13.50 (23.99)
Mean number of dementia patients with psychotropics[2] (SD)	1.34 (3.64)
Share of dementia patients with psychotropics (%, (SD))	7.34 (16.93)
Patients (n)	**164,673**
Mean age of patients (SD)	81.83 (4.62)
Female of dementia patients (%, (SD))	56.87 (32.29)
Mean number of patients with polypharmacy (SD)	4.67 (8.27)
Physician network (n)	**25,011**
Mean number of peers	14.11 (16.85)
Share of psychotropics prescribing[3] (%, (SD))	10.82 (5.33)

Abbreviations: SD, standard deviation

[1] Dementia patients to whom the physicians prescribed any medication.

[2] Dementia patients to whom the physicians prescribed psychotropics (no psychotropic use prior 12 months).

[3] Share of dementia patients to whom the peer networks' physicians prescribed psychotropics.

To estimate the influence of peer networks, we used two criteria to define physicians' peer relationships: 1) patient-sharing and 2) regional proximity. Both criteria were obliged to fulfil for the physicians to be defined as peers. For patient-sharing peer relationships, we considered two physicians to be part of the same network if they had both prescribed medication to the same dementia patient within a calendar year. The average number of shared dementia patients was 2.27 (median, 1). Regional peer relationships were established when physicians practiced in the same local authority

during a calendar year, based on where the majority of their patients resided. Each physician had their own peer network, with some physicians belonging to multiple networks, while others had no network at all (Figure 3).

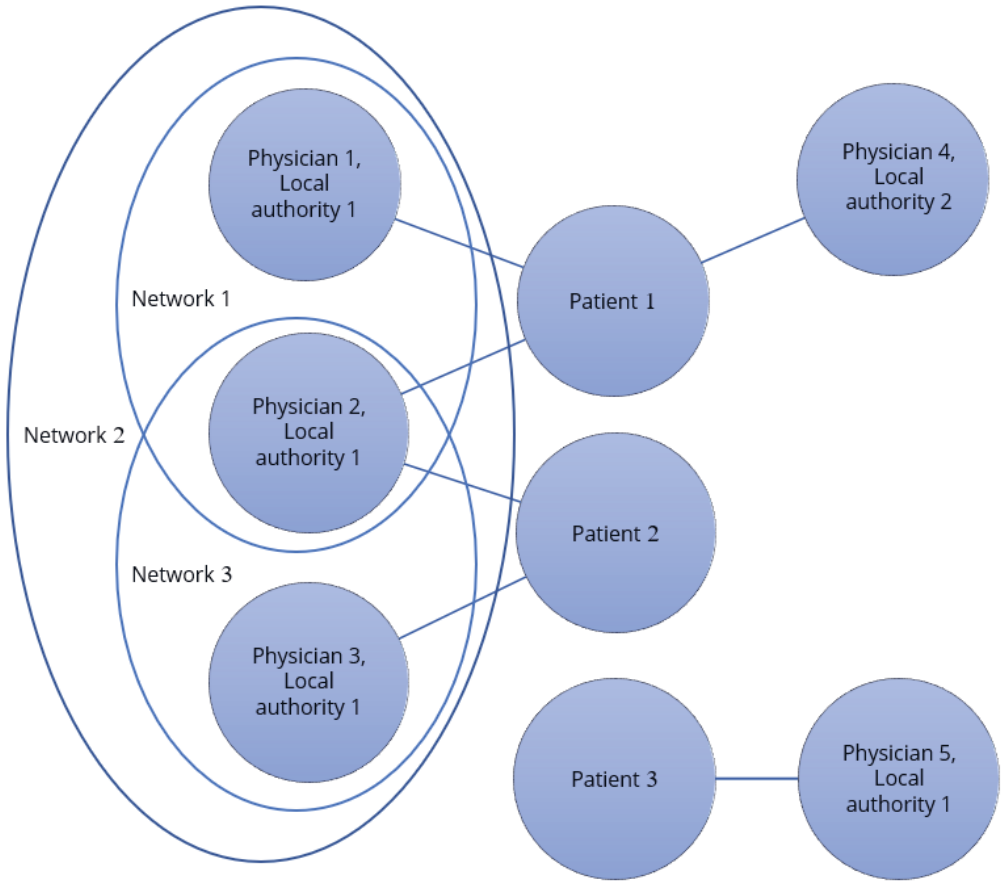

Figure 3. Definition of physician networks

For instance, in Figure 3, physicians four and five have no network, and physician two is part of the networks of physicians one and two. We defined physician *i*'s peer network in year *t-1* as all physicians, other than physician *i*, who shared at least one dementia patient and the same local authority. Furthermore, we calculated the share of psychotropic

prescription patients among the dementia patients for physician *i*'s network, and if the physician had no network, this value was marked as missing.

6.3 Outcome measures

This dissertation provides a comprehensive overview of the outcomes that can be used to evaluate implementation strategies for reducing PIM use in older people. In the scoping review (Article I), we introduced various implementation outcomes based on the framework of Proctor et al. (2011) and explored how they have been utilized in the research literature concerning PIM prescribing.

In Articles II–IV, we delved deeper into outcomes that are suitable for health economic evaluation of implementation strategies. We used QALYs as the outcome to evaluate the cost-effectiveness of the educational intervention in Article II. In the registry-based studies (Articles III–IV), we assessed the implementation of the publication of the Finnish Current Care Guidelines on Memory Disorders using outcomes based on medication purchases from the Prescription Register.

Scoping review of evaluations of implementation strategies for reducing PIM prescribing in older people

The outcomes in the scoping review (Article I) were the implementation outcomes defined in the framework of Proctor et al. (2011): acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability. We decided to use the implementation outcomes by Proctor et. (2011) because the framework is suitable for different healthcare settings, and it was the only one of the few including implementation costs.

From the publications included in the scoping review (Article I), we extracted the following information on implementation evaluation:

authors' concept of process evaluation, study design, healthcare professionals, patients, implementation outcomes and results. We compared the process evaluation concepts of the authors of the included publications with those of Proctor et al. (2011). In addition, we extracted the following data: study years, country, context, PIM criteria, implementation strategy (Santos et al., 2019), organizer, status (mandatory/non-mandatory implementation strategy) and follow-up.

Cost-effectiveness analysis of an educational intervention

In Article II, we used QALYs as the primary health outcome, which were derived from area under a curve (AUC) calculation for the HRQoL-values from the baseline to the last follow-up. HRQoL was assessed using the 15D instrument during the effectiveness study (Pitkälä et al., 2014). HRQoL scores of the weighted 15D index range from 0 to 1, with one being full health and zero being death (Sintonen, 2001). The assessments were performed by interviewing the residents, or the closest proxy (e.g., primary nurse) if dementia was moderate to severe, at the baseline and at 6- and at 12-month follow-ups using the same procedure. The AUC method assumes a linear change between the HRQoL-values at 0, 6 and 12 months. For those participants who died between the 6- and 12-month follow-ups, we assumed the life years gained to be 6 months, and for those who died before the first follow-up, we assumed the life years gained to be 3 months.

In addition, we used intervention cost and costs of healthcare utilization to evaluate the cost-effectiveness of the educational intervention from a healthcare perspective. The healthcare services included: days spent in assisted living facilities, emergency department visits, outpatient visits, hospital ward and primary care ward days. Medication costs were not included because we found no difference in costs between the groups at the 12-month follow-up in our previous study (Aalto et al., 2022). We calculated the intervention costs, which included time use of the recipients (participating nurses, physician, and geriatrician) and the implementer

(educating geriatrician), and implementers' travel expenses and preparation costs. Study materials were offered electronically at zero cost.

We valued the work hours of the implementation recipients and the participants' healthcare utilization according to the National unit costs of social and healthcare in Finland (Kapiainen et al., 2014). Costs were calculated during the 12-month follow-up, and baseline costs for both groups were assumed to be zero, and therefore mean costs were divided by person-years (pyrs). All costs were expressed in euros (€) in 2019 prices and neither costs nor outcomes were discounted.

Registry-based patient level study

In Article III, we evaluated the relationship between the publication of the Finnish Current Care Guidelines on Memory Disorders and the treatment of BPSD. The main outcome variable was the monthly psychotropic user rate of the anti-dementia medication users. Psychotropics were classified as antipsychotics (ATC-N05A), antidepressants (ATC-N06A), anxiolytics (ATC-N05B), hypnotics (ATC-N05C) and antiepileptics (N03AF02, N03AG01, N03AX16).

We defined 'use periods' to analyse the monthly psychotropic user rates. Each individual's first psychotropic purchase was the beginning of a use period. Each individual was observed for 90 days and if s/he had at least one psychotropic purchase during the period, it was extended by a further 90 days, otherwise it ended. The maximum length of the use period (90 days) was based on the reimbursement regulation in Finland, which states that individuals can buy medicine for no more than 3 months treatment at one time (Reimbursements for medicine expenses, 2022). Data included information about package size and the number of packages but did not include the daily doses or individual's purchase patterns, and we assumed that they used one unit per day (Rikala et al., 2013). The end of a use period was defined based on the medicine's package size multiplied by the number of packages, and it was limited to between 7 and 100 days. An

example of the determination of a random individual's use period is presented in Article III, Figure 1.

In addition, we conducted a secondary analysis which concerned individuals who had no psychotropic purchases during the 12 months prior to the measurement month (the monthly psychotropic new user rate). In Finland, psychotropic prescriptions are valid for one year and individuals may purchase prescription medications without an up-to-date physician assessment.

Registry-based physician level study

In Article IV, we evaluated annual psychotropic prescribing on a physician level and the outcome was the number of new prescriptions of psychotropic per physician by year. The psychotropics were classified using the ATC classification system described in the previous registry-based patient level study section. We considered only new prescriptions of psychotropics when the patient had no psychotropics prescriptions one year prior to the date of the prescription of interest. The context of withdrawing a pharmaceutical treatment already in use (deprescribing) is different to the context of not starting a treatment (de-implementation) (Raudasoja et al., 2022; Reeve et al., 2015). Deprescribing is more specifically defined by Reeves et a. (2015) as "the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes". In addition, including only new prescriptions of psychotropic avoids possible bias in the prescribing decision. For example, if a patient already had an existing prescription for antipsychotics and did not need a new one, the physician naturally would not prescribe it.

6.4 Methods and statistical analysis

In this dissertation, we used four different methods to evaluate implementation strategies for reducing PIM in older people. A scoping review (Article I) helped to synthesize previous studies and to find gaps in knowledge. In Article II, we used cost-utility analysis to evaluate the cost-effectiveness of an educational implementation strategy in assisted living facilities. In Articles III and IV, we evaluated the implementation of the Finnish Current Care Guidelines on Memory Disorders using quasi-experimental designs and register data. In Article II, the statistical analyses were performed using Stata statistical software version 15 (StataCorp, College Station, TX). In Articles III and IV, the statistical analyses were performed using R V4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). We used the package "fable" (O'Hara-Wild et al., 2021) in Article III, and the package "fixest" (Berge, 2018) in Article IV. In all the Articles, we considered a p-value of <0.05 statistically significant.

Scoping review of evaluation of implementation strategies for reducing PIM prescribing in older people

A scoping review is suitable for mapping the key concepts of a research area and clarifying the working definitions and conceptual boundaries of the topic. Scoping review differ from narrative or literature reviews in that the scoping process requires analytical reinterpretation of the literature (Levac et al., 2010). In this scoping review (Article I), we followed the reporting guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). The intent of the PRISMA-ScR is to guide scoping review writers to develop understanding of the relevant terminology, core concepts, and key items (Tricco et al., 2018). Our scoping review included: 1) identifying the research question, 2) identifying relevant publications, 3) selecting publications, 4) data extraction, and 5) summarizing the findings.

We mapped the studies based on different implementation strategies (Santos et al., 2019) using the implementation outcome framework of Proctor et al. (2011) in order to clarify the concepts and discover potential gaps in the knowledge of implementation evaluation related to the use of PIMs in older people. We compared the process evaluation concepts of the authors of the included publications with those of Proctor et al. (2011).

We categorized the included publications by implementation outcomes (Proctor et al., 2011) and described the evaluation of the different implementation strategy categories (Santos et al., 2019), focusing on the study designs, viewpoint, and implementation outcome measures. We considered the meaning of these findings and discussed implications for future research.

Cost-effectiveness analysis

The type of economic evaluation in Article II was cost-utility analysis as the health outcome; QALY derived from HRQoL was a generic measure of health gain. We estimated the ICER, which was, in this cost-effectiveness analysis, the ratio of the mean difference in total costs to the mean difference in QALYs between the intervention and control groups during the follow-up.

The equation for ICER was

$$= \frac{\text{QALY intervention} - \text{QALY control}}{\text{COST intervention} - \text{COST control}}$$

where the incremental QALYs were the difference in QALY gain during the 12-month follow-up between the intervention and control groups, and incremental costs were also calculated during the 12-month follow-up. The ICER can serve as a basis for decision-making. The ICER itself may be negative or positive, and to interpret it accurately, the changes in costs and QALYs were reported separately.

If the implementation strategy is less costly and more effective than the control, it is considered dominant and cost-effective. Conversely, if the implementation strategy is more costly and less effective than the control, the control is dominant, and the implementation strategy is not cost-effective. When the implementation strategy is more costly and more effective, the cost-effectiveness depends on the decision-makers' willingness to pay (WTP) for the extra unit of effectiveness. On the other hand, if the intervention is less costly and less effective, the cost-effectiveness is determined by the decision-makers' willingness to accept (WTA) compensation for the lower effectiveness. These decision categories were represented on a cost-effectiveness plane in this study (Drummond et al., 2015, p.41–76; Rotteveel et al., 2020).

The cRCT design of our study caused some issues that required consideration in the analysis. The participants were not randomly allocated to the intervention group and instead, the wards were randomly allocated as intervention and control wards. This is typical for implementation strategy studies where the implementation recipients are randomized but patients' health outcomes are measured (Miller et al., 2020). Consequently, the participants characteristics at the baseline differed in some measures (Table 3). We tested the correlation of the clusters' sizes and participants' baseline characteristics with QALYs and costs and only 15D score and age were significantly correlated with QALYs and costs. There was no correlation (intraclass correlation coefficient -0.15 for QALYs and -0.16 for costs) within a cluster, and individuals were independent.

We attempted to address the clustering issue with propensity score matching, but this proved impractical due to the small sample size and the outcomes being similar to our primary results. Additionally, we explored the use of a DiD model, which would have been suitable for accounting for the cluster structure, but the assumed baseline cost of zero euros in both groups made it challenging to calculate a random-coefficient linear regression model. As an alternative, we employed bootstrap analysis, adjusting for 15D score and age at the baseline (Gomes et al., 2012).

In addition, we acknowledged the skewed distribution of costs at 12 months and created a bootstrapped cost-effectiveness plane for incremental costs and effects utilizing 5000 sub-samples. To address potential uncertainties in the analysis, we performed one-way sensitivity analyses, varying costs and effectiveness in the intervention group by 15% in either direction, as the results could be sensitive to these parameter values. Furthermore, due to the high participant attrition caused by advanced age and mortality, we conducted sensitivity analysis including only participants who were alive at the end of the follow-up.

Registry-based patient level study

In Article III, we used a three-phased ITS design to evaluate the changes in levels and trends of psychotropic use before and after the publication of the Finnish Current Care Guidelines on Memory Disorders. In September 2016, the Finnish Medical Society Duodecim published an article about non-pharmacological treatments in the care of BPSD (Koponen & Vataja, 2016) and in January 2017, they published the guidelines on the treatment of BPSD. In addition, Duodecim supported the dissemination of the guidelines by providing educational material and organizing short education events at two Finnish Medical Conventions in 2017 (Current Care Guidelines, 2017).

The aim of forecasting time series data is to estimate how the sequence of observations continues. ITS methods use aggregate data over equally spaced time intervals before and after the intervention timepoint, and the key assumption is that the trend before the intervention can be extrapolated to predict the trend in a situation where intervention would not occur (Hategeka et al., 2020, Jandoc et al., 2015). In the three-phased ITS analysis, we used the monthly psychotropic user rate as the outcome. The monthly prevalence of all psychotropics were evaluated from January 2009 through to December 2020. The study period was divided into three phases: before guideline publication (pre-intervention period from January 2009 to September 2016, n=93), time between guideline publications

(intervention period from October 2016 to January 2017, n=4), and after guideline publication (post-intervention period from February 2017 to December 2020, n=47).

We observed seasonality, autocorrelation and non-stationary white noise in the data (Article III, Supplementary Figure 1). Therefore, we used the seasonal ARIMA model, which considers these non-stationarity issues (Schaffer et al., 2021). In the ARIMA model, we estimated changes in levels (step intervention) and slopes (ramp intervention) of the monthly psychotropic user rates. The seasonal ARIMA model is expressed as:

$$(p, d, q) \times (P, D, Q)s$$

where p is the order of the autoregressive part of the model, d is the degree of non-seasonal differencing, q is the order of the moving average part of the model and s is the seasonality. D, Q and P are the terms for the seasonal component (Schaffer et al., 2021). We observed seasonality monthly (s=12) and used the Hyndman-Kahandakar algorithm to select the optimal seasonal ARIMA model. We evaluated the model fit by looking at residual plots and using a Ljung-Box test for autocorrelation in residuals.

In addition, we assessed how the monthly psychotropic user rate would have evolved without the publication of the Finnish Current Care Guidelines on Memory Disorders by fitting the seasonal ARIMA model to data preceding the publication and using the model for predicting user rate for the post-intervention period. Subsequently, we plotted the counterfactual forecasted trend with a 95% prediction interval along with the actual observed trend.

The time needed for the guideline recommendations to reach the physicians was unknown. Therefore, we tested the robustness of our findings by setting the intervention timepoint to January 2018. In addition, we conducted a robustness check in which we excluded the year 2020 because COVID-19 might have increased medication use in this population (Finnish statistics on medicines, 2020).

Registry-based physician level study

We used a fixed-effect Poisson model with a physician fixed-effect (Wooldridge, 2010) to study variation in psychotropics prescribing before and after the publication of the Finnish Current Care Guidelines on Memory Disorders in January 2017. Additionally, we examined the influence of physician peer networks on psychotropic prescribing. Physician peer networks may not be independent of unobserved physician characteristics that could influence prescribing practices, which may result endogeneity of the peer network. To address potential self-selection of physicians' peer networks, we included physician fixed effects in our regression model. To account for simultaneity, the peer network of physician *i* was considered from the previous year (*t-1*). The reduction in new prescriptions of psychotropics for the treatment of BPSD corresponds to guideline adherence and, therefore, de-implementation of low-value psychotropics prescribing. In our model, the dependent variable y_{it} represents the number of dementia patients with psychotropics prescriptions from physician *i* in year *t*.

Since count variables like the number of prescriptions are discrete and cannot have values less than zero, we utilized a Poisson fixed-effect model (Wooldridge, 2010). We estimated five different Poisson fixed-effect models to explore prescribing influenced by the Finnish Current Care Guidelines on Memory Disorders (models 1 & 2), prescribing influenced by peers (models 3 & 4), and prescribing influenced by peers and moderated by the guidelines (model 5). We used a guideline dummy as a predictor variable $guidelinedummy_{it}$ that takes the value 0 before year 2017 and 1 otherwise (models 1-5).

We identified peer network influence in two ways. First, by determining the number of physicians in the peer networks and investigating if a larger number of physicians in the peer network, represented by $peernumber_{it-1}$, influenced psychotropics prescribing (model 3). The $peernumber_{it-1}$ was divided by 10 to avoid inoperably low coefficient values. Second, by determining the peer network's share of psychotropics prescribing and

investigating if increasing sharing, represented by $peerprescribing_{it-1}$, influenced psychotropics prescribing (model 4). Last, we examined the heterogeneity with an interaction of the guidelines and peer influence, represented by $guidelinedummy_{it}$ * $peerprescribing_{it-1}$ (model 5).

The fixed-effect Poisson model (5) for y_{it} was:

$$\log y_{it} = \beta_1 guidelinedummy_{it} + \beta_2 peernumber_{it-1} + \beta_3 peerprescribing_{it-1} + \beta_4 guidelinedummy_{it} * peerprescribing_{it-1} + \boldsymbol{\gamma z_{it}} + \alpha_i + \log n_{it}$$

where the dependent variable y_{it} was the number of dementia patients with psychotropics prescriptions from physician *i* at year *t*. β_x were the coefficients of the guidelines' publication and peer network influence. α_i refers to the physician fixed-effect, which was any fixed endowment in the physicians, which were unit-specific, unobserved, and time-invariant. The variation in the number of dementia patients treated by physician *i* may influence psychotropics prescribing, and we adjusted the model with the exposure of dementia patients $logn_{it}$. Low-value psychotropic use in the dementia population was associated with higher age and multimorbidity (extensive polypharmacy) (Brett et al., 2018). To control for patient heterogeneity, we adjusted the fixed-effect models (2-5) with the following variables that vary over time: physicians' patients' mean age, share of female patients, and share of patients on extensive polypharmacy (patients using ≥10 medications (ATC-class) in a calendar year), represented by the vector z_{it}. We used clustered standard errors in the fixed-effect models to allow for correlation between observations within physicians. Estimates of the models are in the logarithmic scale and the percentage change in the original scale is calculated as: 100·(exp(y)−1).

To test the robustness and consistency of our findings, we applied the ordinary least square (OLS) fixed-effect model. To test endogeneity of the peer network, we applied instrumental variable (IV) estimation, where the instrumental variable was peer physicians' peer network. In addition, we

conducted sensitivity analyses with stronger patient-sharing ties, with a minimum number of two shared dementia patients, to test the validity of the patient-sharing peer relationship threshold.

6.5 Research ethics

This dissertation was guided by the general ethical principles of the Finnish Advisory Board on Research Integrity (2019). We examined the data objectively, considering the factors that might have influenced the results, following that the accuracy of the results may be trusted. In addition, we noted that not all factors that may have influenced the results were available from the data. When publishing the results, we considered different perspectives and the generalizability of the findings and discussed the possible bias and limitations of the data and analyses. The results of the Articles were reported transparently, and the researchers' contributions and possible conflicts of interest were considered.

In Article II, the data was collected from the study participants and from the Care Register for Health Care (HILMO). The collection and use of the data were approved by the Ethics Committee of the Helsinki University Central Hospital. Written informed consent was obtained from the residents and/or their closest proxy at the time of the cRCT in 2011–2012. In addition, all study procedures were consistent with good clinical practice and the World Medical Association Declaration of Helsinki.

Articles III and IV were based on register data, and thus, according to Finnish legislation, no ethics committee approval was required as the data were pseudonymized by the register maintainers before being sent to the research team. In addition, no information was obliged to be provided to data subjects when registry-based personal data is processed for scientific or historical research purposes (Regulation (EU) 2016/679). We obtained appropriate permissions to access the data from each register maintainer: 1) the SII of Finland, 2) the Finnish Institute for Health and Welfare (THL), and 3) Statistics Finland.

The study population's personal information was anonymized by Findata during data collection, and we had no access to any original personal identification numbers. All analyses for Articles III and IV were conducted within the Findata Kapseli environment that complies with security regulations and using the protected network facilities of the University of Eastern Finland. All results were checked by Findata Research Services before they were sent from the Findata Kapseli environment and published in the Articles or in this summary. In the registry studies, the final analyses were not on a medication user level and there was no risk of individual's information being recognized or their identity revealed in any manner.

7 Results

7.1 Conceptualizing evaluations of implementation strategies for reducing potentially inappropriate medication prescribing in older people

The scoping review (Article I) included 29 publications of 5,395 identified in the search. The included publications were published during the years 2012–2019, and some of them were from the same research projects. All implementation strategy categories were represented in this review (Table 6). However, the most used implementation strategy category was multidisciplinary intervention and only one publication included other interventions, which examined guideline development and dissemination. The publications used ten different PIM criteria and a variety of countries and healthcare settings were covered. The characteristics of the included studies are represented comprehensively in Article I.

The framework outcomes of Proctor et al. (2011) were mostly covered, except fidelity, and eight publications evaluated multiple implementation outcomes. Most of the evaluations took place at the initial stages of the process (acceptability, adoption, appropriateness, and feasibility) and they were often examined along with the short-term (<12 months) effectiveness of the intervention. Adoption and feasibility were evaluated in ten publications, acceptability in nine publications, and appropriateness in six publications. Penetration and cost-effectiveness were evaluated in one study each and sustainability in two studies.

We used the framework by Proctor et al. (2011) in grouping and conceptualizing the implementation outcomes of the publications. The similarities and differences in the conceptualizations between the authors of the publications and our conceptualizing based on the framework of Proctor et al. (2011) are presented in Table 6.

Table 6. Conceptualizing the implementation evaluation compared to Proctor et al. (2011).

	Similar to Proctor et al. (2011)	**Effectiveness/ cost-effectiveness**	**Feasibility**	**Implementation**	**Process evaluation**	**Usability**	**Adoption**	**Acceptability**	**Quality improvement**
Acceptability	Medication review (2) Computerized system (1)	Medication review (1), Multidisciplinary (1), Computerized system (1)	Medication review, (1), Educational (1)						
Adoption	Multidisciplinary (2), Computerized systems (2), Other (1)	Educational (1)		Multidisciplinary (3)	Multidisciplinary (1)				
Appropriateness	Computerized system (1)		Computerized system (1), Educational (1)		Multidisciplinary (1)	Educational (1)	Multidisciplinary (1)		

Table continues

	Similar to Proctor et al. (2011)	Effectiveness/ cost-effectiveness	Feasibility	Implementation	Process evaluation	Usability	Adoption	Acceptability	Quality improvement
Feasibility	Medication review (1), Computerized systems (1), Educational (2)			Multidisciplinary (1), Educational (1)	Multidisciplinary (1)		Computerized systems (2)	Medication review (1)	
Fidelity									
Implementation cost		Multidisciplinary (1)							
Penetration									Medication review (1)
Sustainability	Medication review (1), Multidisciplinary (1)								

The implementation evaluation conceptualizations differed in terms of acceptability; three out of nine publications conceptualized their study as an acceptability evaluation. The conceptualization of adoption showed some discrepancies, and the terminology was uniform in only five out of ten publications. Only one out of six appropriateness publications used the term. Conceptualizations also differed in terms of feasibility, and only four out of ten publications conceptualized their study as a feasibility study. The one cost-effectiveness analysis fitted the concept of implementation cost. We conceptualized one study as a penetration evaluation as they measured the share of eligible patients for whom the medication review was coded. The conceptualizations of the publications evaluating sustainability were similar to the framework of Proctor et al. (2011).

The scoping review also aimed at finding gaps in knowledge to help future research. One of our main findings was that long-term evaluations and economic evaluations of implementation strategies for reducing PIM use in older people were rare. Secondly, most of the included publications were from healthcare professionals' perspectives, but the management perspective on implementation was lacking. Third, we made a synthesis of the study designs because implementation can be evaluated with different outcomes and different study designs. In this review, study designs were mainly descriptive, but there were also some observational studies, qualitative studies and cRCTs.

7.2 Cost-effectiveness of an educational intervention for nurses to reduce potentially inappropriate medication use

In Article II, the mean QALYs per participant at the 12-month follow-up (adjusted with baseline 15D score and age) were 0.48 (95% confidence interval (CI), 0.45 to 0.51) in the intervention group and 0.50 (95% CI, 0.47 to 0.53) in the control group (Table 7). The intervention was associated with an average of -0.02 (95% CI, 0.06 to 0.02) lower, but not statistically significant, QALYs per participant compared to the control.

We estimated the mean cost per person-years at the 12-month follow-up (adjusted with baseline 15D score and age) as 40,954€ (95% CI, 38,223€ to 43,686€) for the intervention group and 42,584€ (95 % CI, 39,865€ to 45,302€ for the control group. The intervention was associated with an average of -1,629€ (95% CI, -5,489€ to 2,240€) higher, but not statistically significant, costs per person-years compared to the control group (Table 7). The total cost of the educational intervention was 3,981€, which was 34€/resident.

Table 7. Incremental cost and QALYs of educational intervention compared to the control group during the 12-month follow-up (in 2019 euros).

	Intervention group (n=117)	Control group (n=109)	Mean difference (ICER)
Mean €/pyrs (95% CI)	40,954 (38,223 to 43,686)	42,584 (39,865 to 45,302)	-1,629 (-5,489 to 2,240)
Mean QALYs[1] (95% CI)	0.48 (0.45 to 0.51)	0.50 (0.47 to 0.53)	-0.02 (-0.06 to 0.02)
ICER			83,424 €/QALY (-233,191 to 803,989)

Abbreviations: CI, confidence interval; QALY, Quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

[1]Adjusted with baseline 15D score and age.

The educational intervention was estimated to be less costly and less effective than treatment as usual at the 12-month follow-up, and therefore, the cost-effectiveness of the educational intervention was dependent on the decision makers' WTA. ICER was 83,424€/QALY, and the costs saving was 83,424€ per QALY lost in the intervention group compared to the control group (Table 7).

The bootstrapped cost-effectiveness plane (Figure 4) shows values mostly in the south-west quadrant, demonstrating a positive ICER value. The educational intervention was estimated to be less costly and less

effective than the control. The sensitivity analysis including only participants alive at the end of the 12-month follow-up showed no difference between the groups.

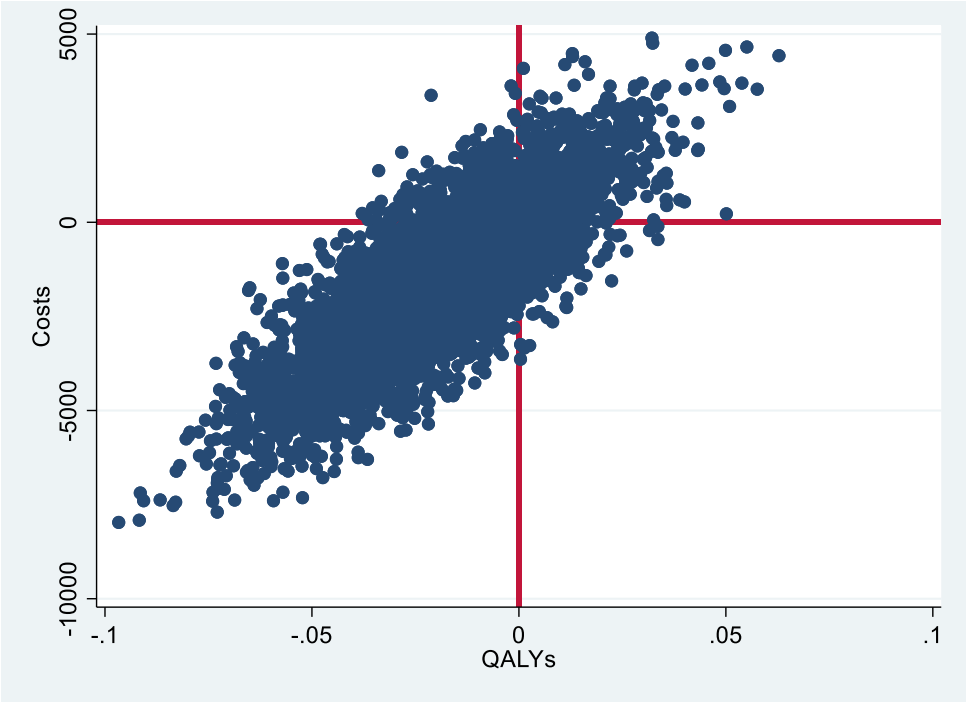

Figure 4. Bootstrapped cost-effectiveness plane of ICER values for educational intervention compared to TAU (Article II).

7.3 Relationship between the Finnish Current Care Guidelines on Memory Disorders and the trend of psychotropics users with dementia

In Article III, the mean monthly psychotropic user rate was 43.8% (standard deviation (SD), 1.76) during the pre-intervention period and 41.7% (SD 0.3) during the post-intervention period (Table 8). In this section, we focus on the results of all psychotropic groups together and the separate results of the five psychotropic subgroups are presented in Article III.

The monthly psychotropic user rate decreased non-significantly during the intervention period (β -0.057, 95% CI, -0.665, 0.550, p=0.853) and did not continue to the post-intervention period (Table 8). We found a non-significant increase in the level (β 0.443, 95% CI, -0.068, 0.953, p=0.091) and slope (β 0.199, 95% CI, -0.103, 0.50, p=0.198) of all psychotropic users during the post-intervention period.

The proportion of new users was naturally lower than the proportion of psychotropic users. The mean monthly psychotropic new user rate was 1.7% (SD, 0.26) during the pre-intervention period and 1.4% (SD, 0.13) during the post-intervention period (Table 8). The level of psychotropic new user rate (β -0.009, 95% CI, -0.284, 0.266, p=0.949) during the intervention period and the level (β 0.044, 95% CI, -0.191, 0.279, p=0.714) were unchanged.

There was no change in the observed trend of all psychotropic users during the post-intervention period compared to the predicted trend (Figure 5). The trend for new users during the post-intervention period were almost unchanged (Figure 6). However, the observed trends were below the mean predicted trends during the post-intervention period, but they fell inside prediction intervals. From Figures 5 and 6, it is noteworthy that the scales are very different because of the different user proportions.

The robustness checks supported the reliability of our findings as the levels and trends of psychotropic users were mostly similar to those in the main findings (Article III, Supplementary materials).

Table 8. Monthly rates and changes in levels and trends of all psychotropic users and new users.

	Pre-intervention period	Intervention period	Step 1	Ramp 1	Post-intervention period	Step 2	Ramp 2
	Mean (SD) monthly rate of users, %	Mean (SD) monthly rate of users, %	Parameter estimate, β (95% CI)	Parameter estimate, β (95% CI)	Mean (SD) monthly rate of users, %	Parameter estimate, β (95% CI)	Parameter estimate, β (95% CI)
All users	(n=93)	(n=4)			(n=47)		
All psychotropics	43.76 (1.76)	41.47 (0.18)	-0.057 (-0.665, 0.550)	-0.167 (-0.461, 0.13)	41.66 (0.33)	0.443 (-0.068, 0.953)	0.199 (-0.103, 0.50)
New users	(n=93)	(n=4)			(n=47)		
All psychotropics	1.721 (0.258)	1.538 (0.062)	-0.009 (-0.284, 0.266)	-0.022 (-0.128, 0.084)	1.366 (0.127)	0.044 (-0.191, 0.279)	0.021 (-0.087, 0.129)

Abbreviations: CI, confidence interval; SD, standard deviation
Step 1 = change in level immediately following publication of the article on BPSD in September 2016
Ramp 1 = gradual slope change relative to the slope in the period prior to publication of the article on BPSD in September 2016
Step 2 = change in level immediately following publication of the guidelines in January 2017
Ramp 2 = gradual slope change relative to the slope in the period prior to publication of the guidelines in January 2017

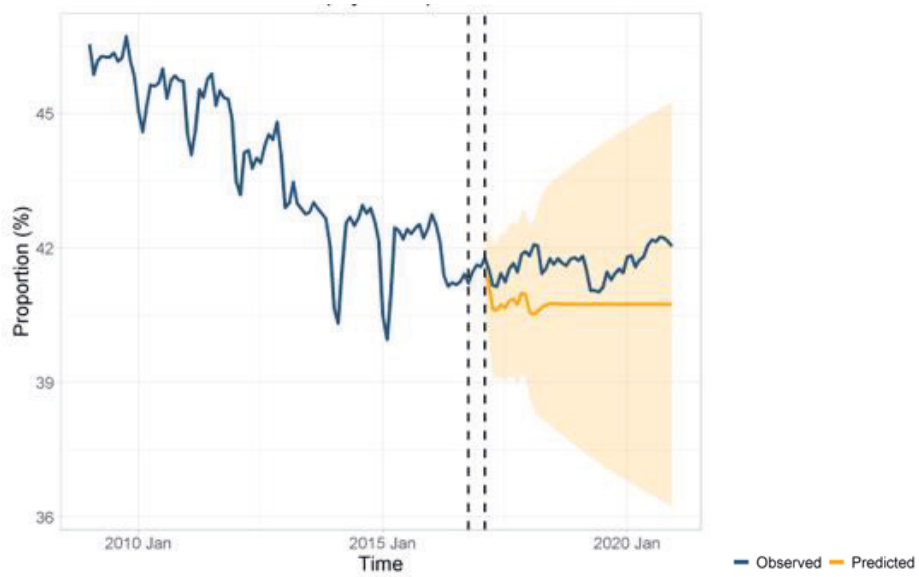

Figure 5. Observed and predicted trends of psychotropics users with 95% prediction intervals (Article III).

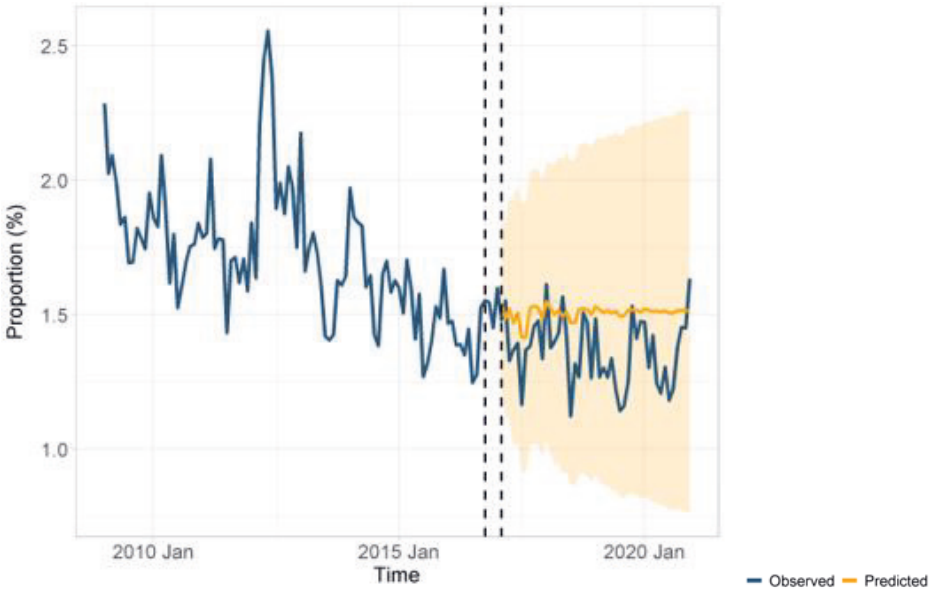

Figure 6. Observed and predicted trends of psychotropics new users with 95% prediction intervals (Article III).

7.4 Influence of physician peer network and the Finnish Current Care Guidelines on Memory Disorders on psychotropic prescribing

In Article IV, we examined the influence of physician peer networks and the publication of the Finnish Current Care Guidelines on Memory Disorders on psychotropic prescribing in the years 2014–2020. The results of the fixed-effect Poisson models (1-5) are presented in Table 9. Model (1) shows that the clinical guidelines' publication was associated with a 0.06 ($p<0.001$) decrease in the psychotropics prescribing on the logarithmic scale, that is, 5.9%. Model (2) shows that the clinical guidelines influence was almost identical when controlled with patient characteristics. We added the number of peers in model (3), and it shows that the number of peers was associated with 0.006 ($p< 0.001$) increase in psychotropics prescribing on the logarithmic scale, meaning that an increase of ten peer physicians in the peer network was associated with a 0.7% increase in the psychotropics prescriptions when controls and time invariant physician characteristics were fixed.

In models (4) and (5) we examined the peer networks' prescribing practice influence on physicians psychotropics prescribing (n=48,434). These models excluded 20% of the observations because in the observed physician had no peer network. Model (4) shows that when the peer networks' share of psychotropics prescribing increased by 1% point it was associated with 0.8% (β0.0081, $p< 0.001$) increase in the psychotropics prescribing. In the model (5) we examined the heterogeneity and interacted the peer networks' psychotropics prescribing rate with the clinical guidelines dummy. After the clinical guidelines were published in 2017 the peer networks' prescribing practice had 0.3% point lower influence on the psychotropics prescribing (β0.0029, $p>0.05$) than before the clinical guidelines, but the result is not statistically significant. The guideline had no influence on those physicians whos' peer networks

prescribed psychotropics to 0 dementia patients before the guideline publication (β -0.0232, p>0.05).

Results of the robustness checks are presented in the manuscript (Article IV) and they supported the results of the main findings. The endogeneity test (IV estimation) confirmed the influence of the peer networks. However, based on the IV estimation, the influence of guidelines was related to uncertainty and may not be exogenous of unobserved physician characteristics (Supplementary Table 4, Article IV).

Table 9. Estimates from Poisson fixed-effect regressions of psychotropics prescribing.

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Clinical guideline (SE)	-0.0606*** (0.0089)	-0.0649*** (0.0089)	-0.0699*** (0.0091)	-0.0557*** (0.0097)	-0.0232 (0.0262)
Mean age of patients (SE)		0.0151*** (0.0023)	0.0150*** (0.0024)	0.0178*** (0.0027)	0.0178*** (0.0027)
Female patients (%, (SE))		0.0035*** (0.0003)	0.0035*** (0.0003)	0.0037*** (0.0004)	0.0037*** (0.0004)
Polypharmacy patients (%, (SE))		0.0026*** (0.0003)	0.0026*** (0.0003)	0.0027*** (0.0004)	0.0027*** (0.0004)
Number of peers (SE)			0.0064* (0.0026)	0.0079** (0.0027)	0.0080** (0.0027)
Peer networks share of psychotropics prescribing (SE)				0.0067*** (0.0014)	0.0081*** (0.0017)
BPSDguideline#Peer networks share of psychotropics prescribing (SE)					-0.0029 (0.0022)
Fixed-Effects:					
Physician id	Yes	Yes	Yes	Yes	Yes
S.E.: Clustered	physician id	physician id	physician id	physician id	physician id
Observations	60,352	60,352	60,352	48,434	48,434
Squared Cor.	0.88021	0.88228	0.88260	0.88498	0.88490
Pseudo R2	0.61620	0.61715	0.61718	0.62143	0.62144
BIC	286,595.2	286,260.7	286,260.0	240,000.9	240,009.2

Note: Estimates are in the logarithmic scale and the percentage change in original scale is calculated as: $100 \cdot (\exp(y) - 1)$.

* p-value <0.05; ** p-value <0.005; *** p-value <0.001; SE, Standard error

7.5 Summary of the findings

We used four different methods and three data sources to evaluate implementation strategies for reducing PIM use in older people with dementia. A short overview of the research questions, study samples, methods, and main findings of the Articles (I–IV) are presented in Table 10. First, we identified a knowledge gap in the implementation evaluation literature regarding economic evaluations and the sustainability of implementation strategies for reducing PIM use in older people. Second, our results indicate that an educational intervention, effective in reducing PIMs in assisted living facilities, was a less costly and less effective implementation strategy, in terms of QALYs, compared with TAU.

Third, the publication of the Finnish Current Care Guidelines on Memory Disorders was not associated with changes in the trend of psychotropic use, but a more favourable association was found with the trend of psychotropics new use among older people with dementia. Lastly, we found that both the publication of the Finnish Current Care Guidelines on Memory Disorders and a physician's peer network influenced new prescriptions of psychotropics.

Table 10. Summary of the Articles.

Article	Research question	Study sample	Methods	Main finding
I	How implementation strategies for reducing PIM prescribing in older people have been studied?	29 research articles published during the years 2000–2019 that met the inclusion criteria of the scoping review.	A scoping review of the literature on the evaluation of the implementation strategies	Long-term and economic evaluations were rare. The conceptualization of the evaluation was indetermined.
II	What is the cost-effectiveness of an educational intervention for nurses to reduce PIM use and its impact on QALYs compared to treatment as usual?	Residents of 20 wards in assisted living facilities in Helsinki were cluster-randomized to intervention (n=118) and control groups (n=109) during the years 2011–2012.	Cost-effectiveness analysis of an educational intervention (cRCT)	The educational intervention was estimated to be less costly and less effective in terms of QALYs compared with TAU.
III	What is the relationship between the publication of Finnish Current Care Guidelines on Memory Disorders and the trend of psychotropic use in older community-dwelling people with dementia?	Community-dwelling Finnish people aged ≥65 years with anti-dementia medication during 2009–2020 (n=217,778).	Three-phased ITS design to evaluate the changes in levels and trends of monthly (n= 144) psychotropic user rates	Publication of the guidelines was not associated with the overall psychotropic use, but more favourable association was found with new users.
IV	What is the influence of the physician peer network and The Finnish Current Care Guidelines on Memory Disorders on psychotropic prescribing practice?	Physicians who prescribed any medication to ≥1 dementia patient not on psychotropic medication 12 months prior (n=25,533) during the years 2014–2020.	Poisson fixed-effect model with physician fixed effect to evaluate the influence of physician peers and guideline on prescribing of psychotropics.	Both, guideline publication and the physicians peer network had influence on the psychotropics prescribing.

8 Discussion

8.1 Interpretation of the results

In this dissertation, we evaluate implementation strategies for reducing PIM use in older people with dementia using cost-effectiveness analysis and quasi-experimental study designs. Dementia is a global health issue, and development of effective implementation strategies could enable more efficient targeting of healthcare resources. Interest in implementation, and de-implementation, has grown in recent decades and a need for health economic evaluation has been recognized. Rather than providing a solution for an optimal implementation strategy or resolving the barriers to high-quality dementia care, this dissertation sheds light on the issues related to translating evidence into practice in dementia care.

In our scoping review, all publications (n=29) evaluating implementation strategies for reducing PIM use in older people included were from the 2010s (Article I). The implementation outcomes by Proctor et al. (2011) were covered, except fidelity. However, acceptability, adoption, appropriateness, and feasibility were the most frequent outcomes, while evaluations of sustainability, penetration, and implementation cost-effectiveness were rare. The findings are similar to those by Proctor et al. (2023), who reviewed literature of the outcomes by Proctor et al. (2011) over the past 10 years. In addition, in our scoping review, the stakeholder perspective in most of the included publications was healthcare professionals' and the management perspective on implementation was lacking. This supports the understanding that the role of leadership in implementation is rarely examined empirically, despite being frequently discussed (Aarons et al., 2014).

Our original aim was to conduct a systematic review to evaluate simultaneously the effectiveness of reducing PIM use and its implementation process. However, after searching for the literature, we

found the conceptualization of implementation evaluations indetermined and we needed to clarify the concepts first to facilitate the systematic review. In only 15 of the 29 publications in our scoping review, the terminology complied with the framework by Proctor et al. (2011). The heterogeneity of the conceptualization in the research is an indication of the complexity of the implementation process (Powell et al., 2019). It was recently found by Proctor et al. (2023) that only 5.5% of the studies examining implementation outcomes examined them in relation to clinical outcomes.

We found the educational intervention, aimed at helping nursing staff to recognize PIMs and adverse drug events in assisted living facilities, less costly and less effective compared to TAU. The ICER was over 80,000€/QALY, and the cost-effectiveness of the educational intervention was dependent on the decision-makers' WTA (Article II). However, the costs and QALYs, as well as ICER, had wide confidence intervals and the differences between the groups were not statistically significant. The educational intervention was shown to reduce PIM use (Pitkälä et al., 2014), but it seemed to not translate into improvements in QALYs. This finding is consistent with that of an economic evaluation of a multidisciplinary implementation strategy by Gillespie et al. (2017), who observed that improvements in PIM use were not translated into QALY gains.

Furthermore, there is relatively little knowledge on the effects of PIM use on HRQoL or QALYs (Hill-Taylor et al., 2016; Mucherino et al., 2022). These findings emphasize the uncertainty of the evidence base of reducing PIM use. This uncertainty poses a challenge to the decision-making process of de-implementation, as the prioritization should be based on the extent of the evidence base (Prasad & Ioannidis, 2014). However, inappropriate medication use depends considerably on PIM criteria used, and the evidence of the inappropriateness between the medicines differ (Motter et al., 2018; Paulamäki, Jyrkkä, Hyttinen, & Jämsen, 2023). Furthermore, there is a need to differentiate the relationship between the effectiveness of the EBP intervention and its implementation.

The registry-based nationwide quasi-experimental studies (Articles III & IV) were the first to evaluate the implementation of the Finnish Current Care Guidelines on Memory Disorders. We evaluated the relationship between the publication of the guidelines and psychotropics use in Finnish community-dwelling older people with dementia. In Article III, we found no change in the observed trend of all psychotropic users after the publication of the guidelines. However, for psychotropic new users, the observed trends were below the mean predicted trends after publication. This may indicate better adherence to the guidelines at the beginning of BPSD treatment. In addition, the study was the first ITS design study to consider the relationship between clinical dementia guidelines and community-dwelling populations' psychotropic use, while previous studies were conducted solely in nursing home environments. Our findings are rather consistent with those of a study by Valiyeva et al. (2008) in which no reduction was found in the rate of psychotropics use after guidelines and safety warnings. On the other hand, three other studies found an association with a decline in the use of antipsychotics after clinical guidelines (Gallini et al., 2014; Gerlach et al., 2021; Maust et al., 2018).

In Article IV, both the publication of the guidelines and physician peer network had a small influence on new prescriptions of psychotropics. Physician peer network influenced new prescribing of psychotropics in two ways. First, the higher the share of psychotropics prescribing in the peer network was, the higher the prescribing of a single physician was. Second, the wider the physician peer network was, the higher the prescribing of a single physician was. The estimated associations were statistically significant but moderate in size. However, after the guidelines were published the association of physician peer network with higher prescribing was unchanged. This indicates that the clinical guidelines did not reduce unwarranted practice variation. These findings support the social network theory (DuGoff et al., 2018; Rogers, 2003, p.300–365) and the literature on the de-implementation of low-value care, which suggests that the utilization of low-value care may be influenced by other physicians and social environment (Ingvarsson et al., 2020; Niven et al., 2015; Patey et

al., 2021). In addition, the findings reinforce the understanding that more consensus among healthcare professionals to facilitate the de-implementation of low-value care is needed in the context of dementia care.

Dementia is different from most chronic diseases because people with dementia may not be able to provide or utilize information as well as patients in general, which complicates research and practice. The inability to make optimal decisions about care or to monitor the quality of care makes dementia patients more prone to being affected by actions taken by caregivers, physicians and other healthcare professionals and highlights the importance of altruistic agents (Chandra et al., 2023). Therefore, it is critical to identify effective implementation strategies aimed at the caregivers that might reduce the impact of BPSD (Bennett et al., 2021). Based on our finding, there is a need for further research into the determinants of the guidelines' implementation and a need to ensure the availability of non-pharmacological interventions to improve adherence to the clinical guidelines on BPSD treatment and to sustainably implement EBPs.

This dissertation clarifies the similarities and differences of the evaluation of implementation outcomes and economic evaluations of implementation strategies. Implementation science places emphasis on establishing causality (Lewis et al., 2018, p.229–244) and a variety of theories, models and frameworks are applied to understand the complex implementation process (Nilsen, 2015). However, in the studies included in our scoping review, the methods used to evaluate implementation strategies were mainly qualitative or observational. Similarly, Proctor et al. (2023) primarily encountered descriptive analyses of implementation outcomes, while quantitative methods were mainly used to assess adoption, cost, fidelity, and penetration. Implementation evaluation would benefit from investigation of the empirical causal mechanisms through which implementation strategies influence treatment outcomes. In turn, economic evaluation of implementation strategies could gain from context-specific information, which may provide richer insights and a better

understanding of causal relationships in complex settings. This dissertation primarily focuses on economic evaluation and physicians' prescribing decision-making. Apart from economic evaluation of implementation strategies, it is recommended that health economic theories, particularly those exploring stakeholders' behaviour, be more widely utilized in the future.

8.2 Strength and limitations

While this dissertation has several strengths, it is also subject to certain limitations and sources of uncertainty. Our scoping review was the first to examine literature on the evaluation of implementation strategies for reducing PIM use in older people. However, we focused on how implementation process evaluation is studied, and it was not possible to state if there are differences in the success of implementation strategies. The selected framework (Proctor et al. 2011) can expand or limit the consideration of factors in implementation evaluation (Damschroder, 2020; Moullin et al., 2020). We applied a broad search strategy; however, the search may have excluded some potential publications. Authors of the included publications did not always specify which part of the process they were studying, and the categorization was based on the information presented in the publications. Unified concepts in implementation research on PIM use had not yet been established, and there may be publications that we did not identify as implementation evaluations.

In the economic evaluation, we used QALYs as patient outcomes because there was relatively little previous knowledge of the effects of implementation strategies for reducing PIM use on QALYs. However, sensitivity analyses demonstrated the uncertainties related to these findings. When including only participants alive at the end of the 12-month follow-up, no difference was found between the groups. This indicates that differences in costs and QALYs were mostly dependent on mortality, and not on the implementation strategy itself. Furthermore, the measurement

of HRQoL and utilizing QALYs in people with dementia is complicated. QALY is argued to be an unsuitable measure in end-of-life care because preference-based measures of health valued using death as an anchor point might be inconsequential in a patient group in which death is expected imminently, and potentially desired (Normand, 2009). In addition, HRQoL metrics are unable to measure other dimensions of QoL, such as social relations, which may become more important to individuals than health in an end-of-life state (Hughes, 2005). It has been suggested that both patient- and proxy-reported outcomes should be included to measure the effects of end-of-life interventions (Yang et al., 2018). Recent suggestions indicate that a meaningful approach would involve focusing on the care outcomes for both people with dementia and their caregivers, rather than solely on health outcomes. This also involves considering measures of Social Care-Related Quality of Life (SCRQoL) (Rand et al., 2022).

We conducted the economic evaluation and cost calculation years after the effectiveness of the implementation strategy was studied and potentially missed some important details of the information delivery and learning, or opportunity costs to providers and patients partaking in the implementation activities (Gold et al., 2022; Hoomans & Severens, 2014). In addition, we lacked information about organizational outcomes, such as adoption, feasibility, or fidelity (Saldana et al., 2022). The healthcare utilization costs were calculated only during the follow-up and thus, baseline costs for both groups were assumed to be zero. In addition, costs for residents' healthcare service use had some deficiencies and societal costs were not included. However, the healthcare perspective may be more suitable for the economic evaluation of implementation strategies (Eisman et al., 2021).

The strength of our quasi-experimental registry-based studies was that the Prescription Register data covers all community-dwelling people in Finland taking anti-dementia medication and older than 65. In addition, Article IV was the first to use the Prescription Register to examine the influence of physician peer network on psychotropics prescribing.

However, the underlying challenge in the evaluation of clinical guidelines was the lack of a confounding variable, which led to a situation where a causal effect was not observed (Grimshaw et al., 2000; Shadish et al., 2003; Huntington-Klein, 2022). Furthermore, psychotropics prescribing is influenced by many factors, such as when the physician sees the guidelines, the patient visits the physician, or the medication is assessed, which can take months or even years. It was impossible to identify the exact time when each physician was exposed to the guidelines, or if they were exposed at all.

The strength of our ITS analysis (Article II) is that we used the seasonal ARIMA model to reduce possible bias caused by non-stationarity (Schaffer et al., 2021). ITS design does not provide protection against the possible influence of other events (e.g., changes in reimbursements or medication prices) occurring at the same time. However, it is considered reliable design for evaluating the implementation of clinical guidelines. The strength of our analysis in Article IV is that we used a fixed-effect approach to isolate and remove omitted variable bias by including physician-level fixed effects that account for unobserved factors at the physician level. However, it would be beneficial to adjust the model for, example with physician age, gender, and medical specialty, but the Prescription Register lacked such background information about the physicians. In addition, we could not entirely separate whether the influence of the patient-sharing peer network was caused by the physicians' or the shared patients' behaviour. The pressure to prescribe low-value psychotropics may be transferred through the patient who has already been prescribed such medication (Flemming et al., 2023; Koponen et al., 2015).

It is noteworthy that during the follow-up periods of our registry-based studies, the population in assisted living facilities offering 24-hour assistance in a home-like environment increased in Finland while long-term inpatient care decreased (Mielikäinen & Kuronen, 2022). However, the Prescription Register data did not contain the community-dwelling persons' exact form of living and care. Consequently, the register had a higher proportion of older people each year whose medication purchases were

reimbursed by the SII. This may underestimate the change caused by the clinical guidelines in the use of psychotropics in community-dwelling older people, since the prevalence of psychotropic use is higher in institutionalized care (Kirkham et al., 2017; Roitto et al., 2019).

There were some uncertainties related to our analyses of physician peer network (Article IV). Identifying causal peer effects is a challenge due to self-selection and unobserved heterogeneities within a peer group, as well as simultaneity where each physician influences peers just as the peer network influences the physician (Hartmann et al., 2008). We addressed simultaneity by considering the peer network from the previous year and excluding physicians from the calculation of their own peer networks. It is also important to note that peer network formation was not random in our study, and we were unable to control for environmental factors. These factors could have resulted in similar behaviour and outcomes among physicians who networked with individuals similar to them in terms of some unobserved factors. However, we applied the IV approach to check the identification of the physicians' peer network, and the estimation confirmed our finding of the peer networks influence. Furthermore, we formed the physician peer networks by utilizing their dementia patient-sharing networks and the local authority where their patients resided. However, the physicians' peer networks in this study may not represent all their social networks. The identification may be biased because physicians may not be prescribing to the same patients while working in the same clinic and thus, may experience social contagion but not be identified as peers in this study.

In this dissertation, the data we used did not include information about the participants' socioeconomic status and we were unable to examine if the de-implementation of PIMs in older people with dementia was associated with disparities between socioeconomic groups. However, in our previous study, we did find disparities between socioeconomic groups in the initiation of new anti-dementia medicine in Finland (Rantsi & Hyttinen, 2020). Healthcare innovations contribute to the overall well-being of society, but the implementation of healthcare innovations and utilization

of low-value care may be associated with disparities between socio-economic groups (Weiss et al., 2018; Helfrich et al., 2019). Therefore, it would be important to acknowledge possible disparities associated with the implementation of EBPs and de-implementation of low-value care in future studies.

8.3 Policy and practice implications

This dissertation may inform health policy decisions aimed at promoting the quality of care, modifying physician behaviour and reducing unwarranted variation in dementia care. The educational intervention we evaluated demonstrated a positive impact on PIM use which, however, appears to diminish at 12 months. The educational intervention was not provided on a continuous basis and not all nurses in the intervention group participated in the training sessions. Nursing staff turnover was not reported in this study, and it might have influenced the sustainability of the findings. While a higher level of participation could have increased the intervention costs, it might also have led to better effectiveness in the intervention group. The educational intervention's costs were only around 30€/resident, and it can be considered a light and feasible implementation strategy. Therefore, to achieve sustainable implementation, educational intervention targeted at nurses and physicians could be organized on a more continuous basis.

The training sessions aimed to enable nurses to recognize PIMs and adverse drug events; however, it could be more favourable to include knowledge of non-pharmacological interventions in future training sessions. This intervention was conducted in 2012, and in 2016, the Current Care Guidelines on Memory Disorders recommended non-pharmacological treatments in the primary care of BPSD. In addition, more recent knowledge on the de-implementation of low-value care recommends behaviour change techniques for de-implementation and the development of theory-based multilevel interventions that simultaneously

decrease the use of low-value care and preserve the use of appropriate care (Grimshaw et al., 2020). One option is behaviour substitution, which aims to increase the frequency of the substitute behaviour in order to de-implement low-value care, which in this case would be non-pharmacological interventions (Helfrich et al., 2018; Patey et al., 2021). The focus should not be solely on reducing PIM use in older people with dementia; there is a need for the implementation of non-pharmacologic interventions and educating care givers about behavioural and environmental approaches (Kales et al., 2019).

There are many factors influencing the treatment of BPSD, such as carers coping with BPSD, care staff, and the people with dementia. Physicians may recommend non-pharmacological treatments, but their implementation is the responsibility all the staff and there can be a lack of resources or knowledge (Jennings et al., 2018). Complex causes of BPSD should be carefully considered, and the Finnish Current Care Guideline on Memory Disorders recommends personalized care plans in dementia care. Nevertheless, strategies engaging stakeholders in person-centred care and approaches tailored to care givers are barely used and behavioural and environmental approaches should be better integrated into dementia care (Kales et al., 2015, 2019). Despite this, psychotropics use is reasonable in the treatment of BPSD in some acute situations where stakeholder safety may be at risk and thus, reduction in medication use should not be used as the only metric of best practice (Kales et al., 2019). However, the applicability of psychotropics would benefit from stronger evidence in frail older population. Therefore, geriatric patients should be represented more widely in clinical trials of new medicines (Florisson et al., 2020). When evidence of medication efficiency and safety in this sub-population is insufficient, physicians face more uncertainty and are under the influence of beliefs and social networks, which may increase unwarranted practice variation.

We found that 67% of the physicians who prescribed medicine to community-dwelling older people prescribed medicine to those with dementia. This indicates that physicians who are prescribing to people with

dementia may not be specialized in geriatrics. The findings are similar to those of Taipale et al. (2014), who discovered that 48–60% of initial prescriptions of psychotropics given to people with Alzheimer's disease in Finland were prescribed by non-specialized physicians. More centralized dementia care has been sought-after as local authorities have been responsible for offering centralized primary healthcare services to people with dementia (Finnish Ministry of Social Affairs and Health, 2013). It is recognized that continuity of dementia care is associated with safer prescribing and it may improve the quality of care (Delgado et al., 2022), but it appears that prescribing to people with dementia in Finland is rather decentralized.

Local authorities are responsible for dementia care in Finland; however, they may differ in organizing care or the availability of healthcare professionals. Overall, in Finland, the number of physicians has grown in the 21st century but regional variation is considerable, and the availability of physicians is lower in rural areas (Statistics on Physicians in Finland, 2019). However, our findings indicate that the physician peer network has influence on psychotropic prescribing, and we recommend paying more attention to strengthening peer networks which apply the best practices. Routine analysis and sharing information about prescribing practice could support the expansion of peer networks where the best practices are in place.

8.4 Implications for future research

Collectively, the findings of this dissertation were diverse, and the discovered influences of the implementation strategies for reducing PIM use in older people were dependent on the data, outcomes and methods used in the evaluations. We suggest that more research in this field is needed, and to guide future studies, we determine the main implications for evaluations of implementation strategies.

We find that implementation research would benefit from investigating the causal mechanisms through which implementation strategies influence treatment outcomes, and econometric methods may help explain the implementation process in terms of causal mechanisms. However, establishing causal relations of implementation strategies has several issues, discussed in that should be considered in future studies. Most importantly, it can be recommended to apply controlled before and after study design when possible. Overall, we support previous literature on the benefits of transdisciplinary ex ante collaboration between health economics and implementation research to achieve well-designed implementation evaluations (Barnett et al., 2020, 2021; Roberts et al., 2019).

Prescription Register is widely used in medicine utilization research in Finland, and it could be used more widely to evaluate implementation of national guidelines. However, we recommend validating the data in terms of the changes in the service system and higher proportion of older people each year whose medication purchases were reimbursed by the SII. In addition, it is noteworthy that our results may be dependent on the selected indicators for guideline adherence. We examined the proportion of psychotropic users divided into subgroups based on the ATC classification (Article III), as well as the proportion of new psychotropic users (Article III) and the number of psychotropic prescriptions (Article IV). In the future, considering different outcomes, such as psychotropic polypharmacy, could prove beneficial for measuring the implementation of guidelines.

Future research is needed on the barriers to implementing clinical dementia guidelines and the availability of non-pharmacological treatments and implementation strategies to support person-centred BPSD. In addition, in our scoping review, we found that the role of leadership in the implementation of clinical guidelines is rarely empirically examined, despite being frequently discussed (Lourida et al., 2017). It is recognized that management and organizational culture have an

important role in implementation (Aarons et al., 2014), and the management perspective should be examined in the future.

Economic evaluations of implementation strategies are needed in the future; however, they differ from evaluating interventions and require a combination of quantitative and qualitative methods. In this dissertation, we focused on quantitative analyses and recognized the need to facilitate richer insights and better understandings of causal relationships in complex contexts, discussed by Dopp et al. (2019) and Salloum et al. (2022). In future studies, economic evaluations could be enriched with qualitative methods, such as interviews and ethnographic field work. Mixed-methods to collect and track implementation costs and benefits are recommended (Dopp et al., 2019; O'Leary et al., 2022).

We evaluated implementation strategies but did not compare whether there are differences between different implementation strategies. In addition, it may not be a sufficient approach to focus either on evaluating the effectiveness of the EBP intervention or exploring its implementation in real-world settings. Proctor et al. (2023) found that only 5.5% of the studies examining implementation outcomes examined them in relation to clinical outcomes and 5% tested relationships among different implementation outcomes. Future studies should investigate relationships among different outcomes before, during, and after implementation to investigate the long-term impact of implementation (Proctor et al., 2023). There is a need for a better understanding of the simultaneous effect of EBP intervention and implementation process.

9 Conclusions

This dissertation brings together three topical areas of interest: health economics, implementation, and dementia care. Rather than providing a solution for an optimal implementation strategy for reducing PIMs in older people with dementia, we offer guidance on the issues related to implementation in dementia care.

We found that acceptability, adoption, appropriateness, and feasibility were the most frequently studied implementation outcomes, while evaluations of sustainability, penetration, and implementation cost-effectiveness were rare in previous studies. We estimated that educational intervention for nursing staff in assisted living facilities had lower healthcare costs, but no impacts on QALYs were found. In addition, we found that the Current Care Guidelines on Memory Disorders was not associated with reduction in the use of psychotropics in older people with dementia. However, the publication of the guidelines was associated with a reduction in the new prescriptions of psychotropics. Furthermore, physician peer network influenced new prescribing of psychotropics before and after the guidelines.

This dissertation may inform health policy decisions aimed at promoting the quality of care, modifying physician behaviour and reducing unwarranted variation in dementia care. Our findings indicate that clinical guidelines and consensus among healthcare professionals facilitates the inappropriate prescribing for people with dementia. However, there is uncertainty regarding the health outcomes of reducing PIMs in older people with dementia, and further knowledge is needed on the cost-effectiveness of reducing PIM use as well as the cost-effectiveness of the de-implementation process.

The methods used in previous evaluations of implementation strategies were mainly qualitative or observational, and future implementation evaluation would benefit from investigation of the empirical causal

mechanisms through which implementation strategies have impact on treatment outcomes. In turn, economic evaluation of implementation strategies could gain from context-specific information, which may provide richer insights and a better understanding of causal relationships in complex settings. In addition, it is recommended that health economic theories, particularly those exploring stakeholders' behaviour, be more widely utilized in the future.

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ARTICLES

ARTICLE I

Rantsi Mervi, Hyttinen Virva, Jyrkkä Johanna, Vartiainen Anna-Kaisa & Kankaanpää Eila. Process evaluation of implementation strategies to reduce potentially inappropriate medication prescribing in older population: A scoping review. Res Social Adm Pharm. 2022 Mar;18(3):2367-2391. DOI: 10.1016/j.sapharm.2021.04.012. Epub 2021 Apr 18.

ARTICLE II

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ARTICLE III

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ARTICLE IV

Rantsi Mervi, Blankart Katharina, Kortelainen Lauri, Jyrkkä Johanna & Hyttinen Virva. Influence of physician peer network and the Finnish Clinical Guidelines on Memory Disorders on prescribing of psychotropic. Manuscript.

ARTICLE I

Rantsi Mervi, Hyttinen Virva, Jyrkkä Johanna, Vartiainen Anna-Kaisa & Kankaanpää Eila. Process evaluation of implementation strategies to reduce potentially inappropriate medication prescribing in older population: A scoping review. Res Social Adm Pharm. 2022 Mar;18(3):2367-2391. DOI: 10.1016/j.sapharm.2021.04.012. Epub 2021 Apr 18.

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Process evaluation of implementation strategies to reduce potentially inappropriate medication prescribing in older population: A scoping review

Mervi Rantsi [a,*], Virva Hyttinen [a], Johanna Jyrkkä [b], Anna-Kaisa Vartiainen [a], Eila Kankaanpää [a]

[a] Department of Health and Social Management, University of Eastern Finland, Finland
[b] Assessment of Pharmacotherapies, Finnish Medicines Agency, Finland

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ABSTRACT

Objectives: Several implementation strategies can reduce potentially inappropriate medication (PIM) prescribing. Although use of PIMs has declined in recent years, it remains prevalent. Various strategies exist to improve the appropriateness of medication use. However, little is known about the processes of these different implementation strategies. This scoping review aims to investigate how the process evaluation of implementation strategies for reducing PIM prescribing in the older population has been studied.

Methods: We searched for process evaluations of implementation strategies for reducing PIM prescribing in PUBMED, SCOPUS and Web of Science published between January 2000 and November 2019 in English. We applied the following inclusion criteria: patients aged ≥65 years, validated PIM criteria, and implementation process evaluated. The review focuses on decision support for health care professionals. We described the findings of the process evaluations, and compared the authors' concepts of process evaluation of the included publications to those of Proctor et al.(2010).

Result: Of 9131 publications screened, 29 met our inclusion criteria. Different process evaluation conceptualizations were identified. Most process evaluations took place in the initial stages of the process (acceptability, adoption, appropriateness, and feasibility) and sustainability and implementation costs were seldom evaluated. None of the included publications evaluated fidelity.

Multifaceted interventions were the most studied implementation strategies. Medication review was more common in acceptability evaluations, multidisciplinary interventions in adoption evaluations, and computerized systems and educational interventions in feasibility evaluations. Process evaluations were studied from the health care professionals' viewpoint in most of the included publications, but the management viewpoint was missing.

Discussion: The conceptualization of process evaluation in the field of PIM prescribing is indeterminate. There is also a current gap in the knowledge of sustainability and implementation costs. Clarifying the conceptualization of implementation process evaluation is essential in order to effectively translate research knowledge into practice.

Introduction

Medication use in the older population can be classified as potentially inappropriate if the associated risks outweigh the potential benefits.[2] Potentially inappropriate medication (PIM) use is associated with adverse drug events, reduced cognitive and physical functioning, increased falls, hospitalization, and mortality.[3–6] The prevalence of PIM use was estimated to be over 20% in the community-dwelling older population in Europe despite the existing criteria and evidence of adverse events due to PIM use.[7]

Abbreviations: Cluster randomized controlled trial, (cRCT); General practitioners, (GPs); Knowledge translation, (KT); Medication review guidance, (MRG-tool); Potentially inappropriate medication, (PIM); Potentially inappropriate prescribing, (PIP); Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis and Evaluation-Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development, (PRECEDE-PROCEED); Quality improvement, (QI); Reach, Effectiveness, Adoption, Implementation, and Maintenance, (RE-AIM).

* Corresponding author. University of Eastern Finland Faculty of Social Sciences and Business Studies Department of Health and Social Management, P.O. Box 1627, FI-70211, Finland.
E-mail address: mervi.rantsi@uef.fi (M. Rantsi).

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The effectiveness of different implementation strategies for reducing PIM prescribing in the older population is comprehensively studied.[8] Implementation strategies are methods or techniques used to improve adoption and implementation of health care innovations and interventions.[9] In the field of PIM prescribing, they are usually categorized into medication reviews, multidisciplinary interventions, computerized systems, educational interventions, and other interventions[8] (Table 1). Implementation strategies, either alone or combined, can reduce the use of PIMs in different settings especially in short-term, but they are not confirmed to have health benefits.[8,10,11] In addition, the economic impact of PIM prescribing is not known.[8]

Process evaluation is part of implementation research, which seeks to understand the processes and factors associated with successful knowledge translation in a particular setting. Process evaluation aids in understanding the relationship between specific program elements and program outcomes, and produces important information on key aspects to which attention should be paid during implementation.[1,12] Implementation frameworks provide a structure for describing, guiding, analysing, and evaluating implementation efforts.[13,14] Framework developed by Proctor et al.[1] consists of implementation outcomes that can be applied to conceptualize and evaluate successful implementation processes in different health care settings.[13] There are also various other models and frameworks of implementation research and process evaluation aim to describe the process of translating research into practice and explain what factors influence implementation effectiveness (i.e. RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) and PRECEDE-PROCEED (Predisposing, Reinforcing and Enabling Constructs in Educational Diagnosis and Evaluation-Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development)).

Implementation research and process evaluation frameworks include different concepts and operationalize them to varying degrees. Some frameworks are more general, while others are more context or intervention specific. In addition, some frameworks are more comprehensive than others, and the selected framework can expand or limit consideration of factors likely to be important in the implementation process.[14,15] In this scoping review, we use the framework of Proctor et al.,[1] which is suitable for process evaluation in different health care contexts and, in our view, more comprehensive and general than the other frameworks, and therefore suitable for a scoping review. The framework includes eight implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation costs, penetration, and sustainability (Table 2).

The effectiveness and process evaluation of implementation strategies to reduce PIM prescribing need to be distinguished from one other.[8] Implementation outcomes differ from effectiveness outcomes, as they measure the success of the process instead of the intervention effectiveness. Studies of implementation strategies should also focus on the processes and mechanisms, and not only on establishing effectiveness.[16] To our knowledge, the process evaluation of implementation strategies to reduce PIM prescribing has not been previously reviewed. Identifying important contextual issues in the implementation process, such as structural, organizational, and operational factors and barriers, is needed in the field of PIM prescribing. Decision makers need to know which conditions favour successful implementation and where the gaps in knowledge need to be filled by further research.[17]

Table 1
Implementation strategies to reduce PIM prescribing.

Medication review is an exhaustive evaluation and/or a discussion of a patient's medications performed by pharmacist or physician. It includes a systematic assessment of the patient's pharmacotherapeutic needs and prescribed drugs, followed by recommendations to optimize the dosage.
Multidisciplinary intervention refers to a quality improvement initiative or pharmaceutical intervention where the clinical practice of pharmacists is integrated with a multidisciplinary team (physicians, nurses and other members of the health care team) as part of the care process.
Educational **intervention** are educational sessions for health professionals, distribution of educational materials, and training for patients and caregivers.
Computerized systems are designed to support health care professionals in the prescribing. They issue risk alerts and provide information about drug interactions.
Other interventions include for example geriatric medicine services, regulatory interventions, guidelines, deprescription and individualized interventions.

Table 2
Implementation outcomes of Proctor et al. (2010).

Acceptability is the perception that a given intervention is agreeable. Lack of acceptability has been noted as a challenge in the implementation process. Acceptability is more specific than service satisfaction, referencing a particular intervention, while satisfaction typically references the general service experience. Acceptability may be measured from the perspective of various stakeholders, such as administrators, payers, providers, and patients by using different measures, for example semi-structured interviews.
Adoption is the intention, initial decision, or action to try an intervention. Adoption also may be referred to as 'uptake'. It can be evaluated from the perspective of provider or organization in the early or middle state of the implementation process with different measures. It is suggested that adoption is assessed at 6–18 months after initial implementation.
Appropriateness is the relevance or compatibility of an intervention for a given setting (i.e. provider, consumer or perceived fit of the intervention). Appropriateness and acceptability are connected, but a given intervention may be perceived as appropriate but not acceptable. For example, a treatment might be considered a good fit for treating a given condition, but its features may render it inappropriate to the provider.
Feasibility is the extent to which a new intervention can be successfully used or carried out within a given setting. Typically, the concept of feasibility is referred to retrospectively as a potential explanation of an implementation success or failure in recruitment, retention, or participation rates. Feasibility is related to appropriateness, but an intervention may be appropriate for a service setting (intervention is compatible with the setting's mission or service mandate) but may not be feasible due to resource or training requirements.
Fidelity is the degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended by the intervention developers. Fidelity has been measured by comparing the original evidence-based intervention and the implemented intervention in terms of adherence to the programme protocol or amount of programme delivered.
Implementation cost is the cost impact of an implementation effort. The cost of implementing an intervention includes the costs of the intervention, the implementation strategy used, and the service delivery. Cost is essential to studies comparing the cost-effectiveness of various implementation strategies.
Penetration is the integration of an intervention within a service setting. It can be calculated as the share of eligible service recipients who use a service or the share of providers who deliver a given service. Penetration can be evaluated in the mid or late stage of the implementation process.
Sustainability is the extent to which the implemented intervention is maintained or institutionalized within a service setting (the extent to which an evidence-based intervention is integrated into all subsystems of an organization). Sustainability is attaining long-term viability, as the final stage of the diffusion process, when new intervention settles into organizations.

Objective

The aim of this scoping review is to investigate how the processes of implementation strategies for reducing potentially inappropriate medication PIM prescribing in the older population have been studied. We map the studies based on different implementation strategies using the framework of Proctor et al.[1] in order to clarify the concepts and discover potential gaps in the knowledge of implementation process evaluation related to the use of PIMs in the older population.

Methods

Scoping review

A scoping review is suitable for mapping the key concepts of a research area and clarifying the working definitions and conceptual boundaries of a topic.[18,19] Our scoping review included: 1) identifying

the research question; 2) identifying relevant publications; 3) selecting publications; 4) data extraction; and 5) summarizing the results. We followed the reporting guidelines of the PRISMA-ScR statement.[20]

Search strategy

We searched the following databases: Scopus, Web of Science and PubMed for publications dated between January 2000 and November 21, 2019, language restricted to English. Keywords were searched as, for example: elderly AND medication AND rational or inappropriate AND implementation. See APPENDIX A for the detailed search strategy.

Study selection

Inclusion criteria for the scoping review were: 1) patients aged ≥65 years, 2) PIMs defined by validated criteria, 3) decision support for health care professionals, 4) implementation process evaluated, 5) original articles and reviews, and 6) quantitative or qualitative methods. We excluded publications where the rational use of medication was mentioned in the context of other purposes (i.e. adherence, timing, delivery, polypharmacy, no PIM criteria). As the focus of this review is on decision support for health care professionals, we excluded publications where the intervention was based on patient education.

Two authors (MR & VH) screened the data independently according to the inclusion criteria in two steps (Fig. 1. Publication selection process). MR and VH discussed the challenges and uncertainties related to the study selection. A third opinion (JJ) was sought if uncertainty remained.

Data extraction

From the included publications, we extracted the study characteristics: study years, country, context, PIM criteria, implementation strategy, organizer, status (mandatory/non-mandatory implementation strategy) and follow-up. In addition, we extracted the following information on implementation process evaluation: authors' concept of process evaluation, study design, health care professionals, patients, implementation process measures and results.

Two authors (MR & A-KV) independently extracted data from five included publications and determined whether their approach to data extraction was consistent. MR completed the data extraction.

Summary and synthesis

We compared the process evaluation concepts of the authors of the included publications with those of Proctor et al.[1] We categorized the included publications by implementation process outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability (Table 2). In these categories, we described the process evaluation of the five different implementation strategy categories[8] focusing on the study designs, viewpoint, and implementation outcome measures. We considered the meaning of these findings and discussed implications for future research.

Results

Result of the search

The initial search identified 9131 records and after duplicates removal 5395 records remained (Fig. 1). We excluded 5231 records based on the exclusion criteria after reading the abstract. Records were excluded because they did not address PIM prescribing or implementation process evaluation. We retrieved 165 full texts for further examination, of which 46 were assessed for eligibility. Thirteen of the

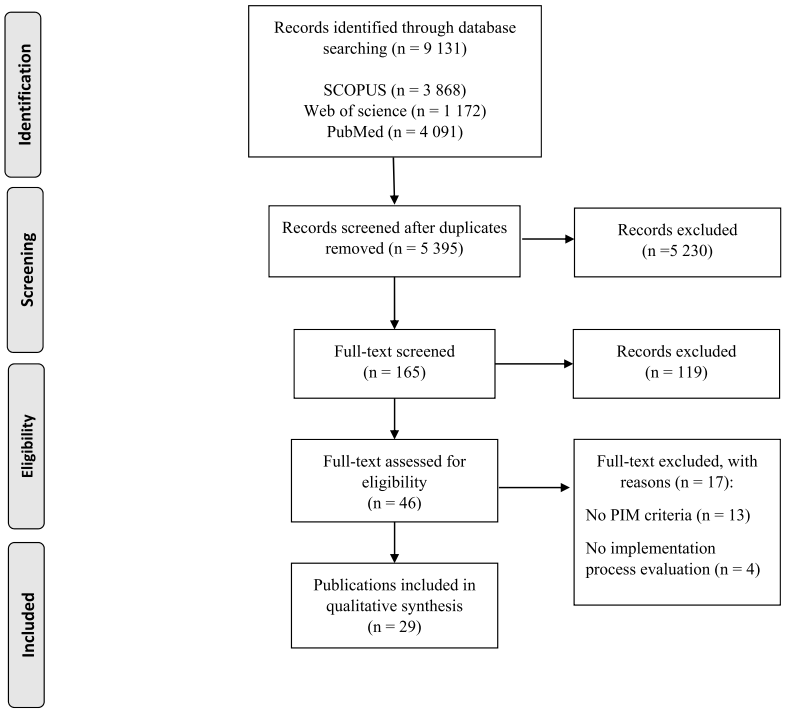

Fig. 1. Publication selection process.

full texts were excluded because PIMs were undefined by validated criteria. Four publications failed to apply implementation process evaluation. Finally, 29 publications met the inclusion criteria (Fig. 1). After screening the reference lists of the included publications, none were included.

Description of included publications

The 29 included publications were published during the years 2012–2019.[21–49] The publications represented all implementation strategy categories and were from 22 implementation strategy studies. In the included publications, the most commonly used implementation strategy category was multidisciplinary intervention.[28–38] Two of these publications were from the OPTI-SCRIPT study,[30,32] two were from an Italian national quality improvement (QI) project[33,34] and two were from the EQUiPPED study.[36,37] Multidisciplinary interventions were mainly QI projects with varying components. Combinations of multidisciplinary teams, medication reviews, web-based programmes and staff education were included alternately in the projects. Seven publications evaluated solely medication reviews,[21–27] five evaluated educational interventions,[44–48] and five evaluated computerized systems.[39–43] Two of the computerized system publications were from the PRIMA-eDS trial[40,41] and one evaluated clinical decision support as a part of the EQUiPPED study.[42] One study evaluated clinical guideline dissemination.[49] Characteristics of the included publications are presented in Table 3.

Used PIM criteria varied, and seven publications used multiple criteria. Most common criteria were the Beers criteria: nine publications used Beers 2012 [21,28,29,31,35–38,42], and five publications used Beers 2003.[25,39,45,47,49] Ten publications used the STOPP/START criteria.[21,25,30,32,35,39,43,44,46,48] All following criteria were used in two separate publications: Swedish National quality indicator for elderly drug use 2003 [27,47], Swedish National quality indicator,[24,48] Ghent Older People's Prescriptions Community Pharmacy Screening (GheOP3S) tool,[22,23] PRIMA-eDS tool,[40,41] and Maio criteria.[33,34] MRG-tool[26] and Priscus[39] were used in single publications.

The included publications represented a variety of countries and health care contexts. Nineteen of the publications were from European countries,[21–25,27,30,32–34,39–41,43–48] six from the United States,[29,36–38,42,49] and three from Canada.[26,28,31] In addition, one publication was from Saudi Arabia.[35] Primary care was the most common environment.[27,30,32–34,38,40,41,44,47,48] In eight publications the environment was hospitals[29,31,35–37,39,42,45] and in six publications the environment was a nursing home.[21,23,25,26,28,46] Only two publications concerned community pharmacy,[22,43] and two covered a combination of hospitals, nursing homes and primary care centres.[24,49]

The implementation strategy was mandatory in ten publications. Regional authorities in Sweden were the organizers in three publications.[24,27,48] Two publications evaluated the same Italian national QI project organized by Emilia-Romagna Region.[33,34] Three publications considered the QI project organized by the Veterans Health Administration in the USA.[36,37,42] One publication evaluated a knowledge translation (KT) strategy mandated by the Quebec government[31] and one evaluated a model of coordinated primary care (Care by Design) introduced by the Capital District Health Authority in Canada.[28] Research groups were the organizers in all other implementation strategies, and thus they were regarded as non-mandatory.

Follow-up time was mainly around twelve months, but some publications had a timeframe longer than one year. The longest follow-up was six years,[34] and in two studies the follow-up was only one month.[44,49] Additionally, four publications had no follow-up period.[24,42,43,48]

Conceptualizing the process evaluation of implementation strategies

We used the framework by Proctor et al.[1] in grouping the publications. Table 4 presents the similarities and differences in the conceptualizations of implementation process evaluation. The framework of Proctor et al.[1] was covered, except fidelity. Eight publications evaluated multiple implementation outcomes.[23,30,37,40,41,43,44,48]

The implementation process evaluation conceptualizations differed in terms of acceptability; three out of nine publications conceptualized their study as an acceptability evaluation.[22,23,43] Four publications conceptualized their study as an implementation effectiveness study, used the term acceptance, and measured the acceptance rate.[25,29,35,39] Cattaruzzi et al.[21] and Franchi et al.[45] conceptualized their publications as feasibility evaluations instead of acceptability, but according to Proctor et al.,[1] they were measuring the acceptability of the implementation strategies.

The conceptualization of adoption showed some discrepancies: the terminology was uniform in only five out of ten publications.[28,33,40,41,49] Three publications used the term implementation, and did not specify which part of the process they studied.[31,36,37] Clyne et al.[30] conceptualized their study as a process evaluation, but also used the terms adoption, useful and feasible and, according to the framework of Proctor et al.,[1] they evaluated adoption, appropriateness, and feasibility. Rognstad et al.[47] conceptualized their study as an educational intervention effectiveness study, although it was similar to the other adoption publications measuring PIM rates.

There were noticeable differences in the conceptualization of appropriateness, and only one out of six appropriateness publications used the term.[41] Two publications conceptualized their study as a feasibility study[38,44] and one as an adoption study.[42] Two publications used the terms usability and usefulness,[30,48] and Clyne et al.[30] conceptualized their study as a process evaluation.

Conceptualizations also differed in terms of feasibility, and only four out of ten publications conceptualized their study as a feasibility study.[26,43,44,48] Two publications used the term implementation, and did not specify which part of the process they studied.[37,46] Foubert et al.[23] conceptualized their study only as an acceptability evaluation, but also studied reasons not to implement accepted recommendations, which fits the feasibility evaluation according to Proctor et al.[1] Clyne et al.[30] conceptualized their study as a process evaluation. Two publications conceptualized their study only as an adoption evaluation, but also studied the barriers to and facilitators of the implementation.[40,41]

The publication by Gillespie et al.[32] was conceptualized as a cost-effectiveness analysis of the OPTI-SCRIPT implementation strategy, and fits the concept of implementation cost [1]. The publication by Ödesjö et al.[27] was conceptualized as a QI study, but as they measured the share of eligible patients for whom the medication review was coded, we conceptualized the study as a penetration evaluation according to Proctor et al.[1] The conceptualizations of the publications evaluating sustainability[24,34] were similar to the framework of Proctor et al.[1]

We summarize the process evaluation publications into five implementation strategy categories. In our analyses, we focus on the study characteristics and report the study designs, viewpoint, and implementation outcome measures (Table 5). The results of the process measure are also presented in Table 5 but are not commented on here. Publications may be presented in Table 5 more than once depending on the studied implementation outcomes.

Acceptability

Acceptability was evaluated in nine publications, and in all implementation strategy categories except other interventions.[21–23,25,29,35,39,43,45] Medication review was the most usual implementation strategy in acceptability evaluation.[21–23,25] Evaluations of acceptability included only descriptive study designs and the viewpoint of health care professionals.

In eight publications the health care professionals were physicians, general practitioners (GPs), or clinicians. In the publication by Chowdhury et al.,[29] health care professionals were health care teams. All publications included pharmacist recommendations except, the publication by Franchi et al. [45] which was an e-learning programme for

Table 3
Characteristics of included publications by implementation strategy.

Publication	Study years	Country	Context (n)	PIM criteria	Implementation strategy	Organizer	Status	Follow-up
Medication reviews								
Cattaruzzi[21] et al., 2018	2013	Italy	Nursing homes (4)	Beers 2012, STOPP/START	Multidisciplinary medication review	Research group	Non-mandatory	10 months
Foubert[22] et al., 2019a	2016–2017	Belgium	Community pharmacies (12)	GheOP3S tool	Multidisciplinary medication review (pharmacist recommendations)	GheOP3S research group (Genth University)	Non-mandatory	11 months
Foubert[23] et al., 2019b	2017	Belgium	Nursing home (1)	GheOP3S tool	Multidisciplinary medication review (pharmacist recommendations)	GheOP3S research group (Genth University)	Non-mandatory	6 months
Kempen[24] et al., 2019	Data up to 2015	Sweden	Hospitals, nursing homes or primary care centres that employed clinical pharmacist	Swedish National quality indicators	Medication review	Region Uppsala	Mandatory	NA
Verrue[25] et al., 2012	NA	Belgium	Nursing homes (2, other control)	STOPP/START, Beers 2003	Medication review	Research group	Non-mandatory	6 months
Wilchesky[26] et al., 2018	2014	Canada	Nursing homes (3)	MRG tool (medication appropriateness for seniors with severe dementia)	MRG tool	Research group (local Health and Social Services Board (HSSB) and CHU de Québec research centre)	Non-mandatory	12 months
Ödesjö[27] et al., 2017	2009–2013	Sweden	Primary care	Swedish National quality indicator for elderly drug use 2003	Medication review with pay for performance payment system	Region Västra Götaland	Mandatory	5 years
Multidisciplinary interventions								
Andrew[28] et al., 2018	2008–2012	Canada	Long-term care facilities (10)	Beers 2012	Model of coordinated primary care in long-term care facilities (LTCF) "care by design"	Capital District Health Authority	Mandatory	3 years
Chowdhury[29] et al., 2018	2014–2015	USA	Medical centre (1 general medical floor)	Beers 2012	Quality improvement intervention	Research group, Baystate Medical Centre	Non-mandatory	18 months
Clyne[30] et al., 2016	2012–2013	Ireland	Primary care general practices (21)	STOPP	Medication review, web-based pharmaceutical treatment algorithms and tailored patient information leaflets (OPTI-SCRIPT)	OPTI-SCRIPT research group	Non-mandatory	12 months
Cossette[31] et al., 2016	2013–2015	Canada	Hospital	Beers 2012	Knowledge translation (KT) strategy	Centre Hospitalier Universitaire de Sherbrooke (CHUS)	Mandatory	3 years
Gillespie[32] et al., 2017	2012–2013	Ireland	Primary care general practices (21, intervention n = 11, control n = 10)	STOPP	Medication review, web-based pharmaceutical treatment algorithms and tailored patient information leaflets (OPTI-SCRIPT)	OPTI-SCRIPT research group	Non-mandatory	12 months
Keith[33] et al., 2013	2007–2009	Italy	Outpatient healthcare Parma Local health authority (LHA)	Maio criteria	Physician-focused, multi-phase, multi-factorial, national quality-improvement project	Parma LHA, Emilia-Romagna Region (RER)	Mandatory	2 years
Lopatto[34] et al., 2014	2005–2010	Italy	Outpatient healthcare Parma Local health authority (LHA)	Maio criteria	Physician-focused, multi-phase, multi-factorial, national quality-improvement project	Parma LHA, Emilia-Romagna Region (RER)	Mandatory	6 years
Mekdad[35] et al., 2019	2014–2016	Saudi Arabia	Hospital cardiology ambulatory care unit	Beers 2012, STOPP/START	Quality improvement project	Research group	Non-mandatory	3 years
Moss[36] et al., 2016	2012–2014	USA	Durham VAMC ED	Beers 2012	Quality improvement initiative (EQUiPPED)	Veterans Health Administration	Mandatory	2 years 10 months
Moss[37] et al., 2019	2011–2014	USA	Durham VAMC ED	Beers 2012	Quality improvement initiative (EQUiPPED)	Veterans Health Administration	Mandatory	2 years 10 months
Vandenberg[38] et al., 2018	2014–2016	USA	Community-based outpatient clinics (4)	Beers 2012	Quality improvement program (IMPROVE)	IMPROVE project	Non-mandatory	6 months
Computerized systems								

(*continued on next page*)

Table 3 (*continued*)

Publication	Study years	Country	Context (n)	PIM criteria	Implementation strategy	Organizer	Status	Follow-up
O'Sullivan[39] et al., 2014	2013–2014	Ireland	Accident & emergency (A&E) department of 810-bed hospital	STOPP, Beers 2003 & Priscus	Structured pharmacist review of medication supported by a computerized decision support system	Research group, Irish University teaching hospital	Non-mandatory	12 months
Rieckert[40] et al., 2018	NA	Germany	PRIMA-eDS trial participant study centres in Germany	PRIMA-eDS tool (EU (7)-PIM list)	Electronic decision support tool	PRIMA-eDS European multicentre trial	Non-mandatory	12 months
Rieckert[41] et al., 2019	2016–2017	Germany, Austria, Italy, UK	PRIMA-eDS trial participant study centres (5)	PRIMA-eDS tool (EU (7)-PIM list)	Electronic decision support tool	PRIMA-eDS European multicentre trial	Non-mandatory	10 months
Vandenberg[42] et al., 2017	NA	USA	Veterans affairs medical centre (VAMC) Emergency department	Beers 2012	Clinical decision support (CDS), part of EQUiPPED	Veterans Health Administration (The largest integrated health care system in the United States, providing care to veterans)	Mandatory	NA
van der Meer[43] et al., 2018	2017	Netherlands	Community pharmacies (47)	STOPP/START, Dutch reference source for pharmacotherapy in older people.	IT-based pharmacist led intervention	Research group	Non-mandatory	NA
Educational interventions								
Cadogan[44] et al., 2018	2015	Northern Ireland	Primary care, general practices (2)	STOPP/START	Educational online video	Research group	Non-mandatory	1 month
Franchi[45] et al., 2014	2011	Italy	Italian National Health Service hospital wards (8, intervention n = 4, control n = 4)	Beers 2003	E-learning and educational programme for clinicians	Research group	Non-mandatory	3 months
Gulla[46] et al., 2019	2014–2015	Norway	Nursing home units (36)	STOPP/START	Medication review including collegial mentoring	COSMOS research group	Non-mandatory	4 months
Rognstad[47] et al., 2013	2006–2007	Norway	General practices Continuing medical education groups (81, intervention n = 41, control n = 40).	Beers 2003, Swedish National quality indicator for elderly drug use 2003	Multifaceted educational intervention	Research group	Non-mandatory	2.5 years
Schmidt-Mende[48] et al., 2018	NA	Sweden	Primary care practices (33)	STOPP/START, Swedish National quality indicators, Norwegian NORGEP criteria	Medication review and educational intervention with financial incentive	Stockholm County Swedish National Board of Health and Welfare	Mandatory	NA
Other interventions								
Bachyrycz[49] et al., 2012	2008–2010	USA	State level managed care organizations (27) (i.e. academic institutions, nursing homes, hospitals)	Beers 2003	Clinical guideline dissemination	Funded by Centre for Medicaid and Medicare Services, performed by HealthInsight New Mexico	Non-mandatory	1 month

NA, Not available; ED, emergency department; MRG tool, medication review guidance.

clinicians for changing clinical practice. Acceptability was mainly measured by GPs' and physicians' acceptance of pharmaceutical recommendations after the medication review.[21–23,25,35,39,43] Chowdhury et al.[29] compared the health care team's acceptance rate before and after the QI project. Franchi et al.[45] measured the opinions regarding acceptability with questionnaires to clinicians. Additionally, two publications explored reasons for GPs' not accepting pharmaceutical recommendations via questionnaires to GPs.[22,23]

Adoption

In total, ten publications evaluated the adoption of the implementation strategies, and only the medication reviews were not represented.[28,30,31,33,36,37,40,41,47,49] The study design of the adoption evaluations varied. Three observational studies had a control group,[31,33,37] and two were observational before-and-after studies.[28,36] Three publications evaluating adoption used a descriptive study design,[30,41,49] one was a cRCT[47] and one a qualitative study.[40]

Six publications were based on patient outcomes.[28,31,33,36,37,47] Of these, five evaluated the adoption of multidisciplinary interventions and one, Rognstad et al.,[47] evaluated educational intervention. Patient outcome was PIM use or potentially inappropriate prescribing (PIP) prevalence, and the follow-up time was two to three years. Four publications had a control group.[31,33,37,47]

The viewpoint was physicians' or GPs' in three publications.[30,40,41] Two of these publications evaluated the adoption of a computerized system as part of the PRIMA-eDS trial. Rieckert et al.[40] conducted a qualitative study in which they interviewed participating GPs in Germany. Later, Rieckert et al.[41] studied the adoption of the PRIMA-eDS tool as a proportion of GPs conducting medication review in four European countries. In the publication by Bachyrycz et al.,[49] the viewpoint was the health authority, and this was the only included publication that evaluated other interventions. They evaluated guideline development

Table 4
Similarities and differences in conceptualizing implementation process evaluation compared to Proctor et al. (2010).

	Similar to Proctor et al. (2010)	Effectiveness/ cost-effectiveness	Feasibility	Implementation	Process evaluation	Usability	Adoption	Acceptability	Quality improvement
Acceptability	Foubert[22] et al., 2019a, Foubert[23] et al., 2019b, van der Meer[43] et al., 2018	Verrue[25] et al., 2012, Chodhury[29] et al., 2018, Mekdad[35] et al., 2019, O'Sullivan[39] et al., 2014	Cattaruzzi[21] et al., 2018, Franchi[45] et al., 2014						
Adoption	Andrew[28] et al., 2018, Keith[33] et al., 2013, Rieckert[40] et al., 2018, Rieckert[41] et al., 2019, Bachyrycz[49] et al., 2012	Rognstad[47] et al., 2013		Cossette[31] et al., 2016, Moss[36] et al., 2016, Moss[37] et al., 2019	Clyne[30] et al., 2016				
Appropriateness	Rieckert[41] et al., 2019		Vandenberg[38] et al., 2018, Cadogan[44] et al., 2018		Clyne[30] et al., 2016	Schmidt-Mende[48] et al., 2018	Vandenberg[42] et al., 2017		
Feasibility	Wilchesky[26] et al., 2018, van der Meer[43] et al., 2018, Cadogan[44] et al., 2018, Schmidt-Mende[48] et al., 2018			Moss[37] et al., 2019, Gulla[46] et al., 2019	Clyne[30] et al., 2016		Rieckert[40] et al., 2018, Rieckert[41] et al., 2019	Foubert[23] et al., 2019b	
Fidelity									
Implementation cost		Gillespie[32] et al., 2017							
Penetration									Ödesjö[27] et al., 2017
Sustainability	Kempen[24] et al., 2019, Lopatto[34] et al., 2014								

and dissemination by observing the use of web-based PIM guidelines.

Appropriateness

Appropriateness was evaluated in six publications.[30,38,41,42,44,48] Of these, five were based on descriptive study designs and one was a qualitative study design.[48] Therefore, none of these studies had a control group. Health care professionals were physicians or GPs in five publications,[30,38,41,42,44] and physicians, nurses and an educating pharmacist in the publication by Schmidt-Mende et al.[48] The publication by Clyne et al.[30] additionally measured appropriateness via patient interviews.

Two of the publications evaluated the appropriateness of multidisciplinary interventions: Clyne et al.[30] studied appropriateness by interviewing GPs and patients about the usefulness of the OPTI-SCRIPT study, and Vandenberg et al.[38] via telephone interviews with primary care physicians. Another two publications evaluated the appropriateness of computerized systems[41,42]: one used a questionnaire for GPs participating in the PRIMA-eDS study[41] and the other used physician interviews.[42] The remaining two publications evaluated the appropriateness of an educational intervention,[44,48] both from the GPs' point of view: Schmidt-Mende et al.[48] analysed two pharmacists' unstructured diaries, which reported GPs' and nurses' views on medication reviews.

Feasibility

Feasibility was evaluated in 10 publications in terms of the barriers and facilitators for implementation at different organizational levels, or as health care professionals' views regarding time consumption. Health care professionals were GPs in five publications,[23,30,40,41,44] and the other five publications also included other health professionals (i.e. pharmacist, nursing staff).[26,37,43,46,48] Most publications used descriptive study designs, but two were qualitative[40,48] and one had an observational study design.[37] There were no control groups when evaluating feasibility. Although the study by Moss et al.[37] had a control group, it was not applied when measuring feasibility.

Two of the publications evaluated the feasibility of medication review. Foubert et al.[23] studied the main reasons for GPs not implementing pharmacists' recommendations. Additionally, the opinions of GPs, clinical pharmacists, heads of nursing homes and staff nurses regarding barriers to the use of the MRG tool were measured in the publication by Wilchesky et al.[26] Feasibility of multidisciplinary intervention was evaluated in two publications.[30,37] Moss et al.[37] conducted a questionnaire survey of resident physicians related to PIM prescribing and the use of Beers Criteria before and after the QI project. Clyne et al.[30] interviewed GPs after the OPTI-SCRIPT implementation regarding facilitators and barriers.

Three publications evaluated the feasibility of computerized systems, two of which evaluated the PRIMA-eDS tool.[40,41] The qualitative PRIMA-eDS tool study investigated the time needed to read the comprehensive medication review (CMR) and GPs' views regarding time consumption.[40] Later, they measured GPs' opinions via a questionnaire in five countries after the PRIMA-eDS study.[41] Additionally, pharmacists' opinions were measured by questionnaires after the IT-based intervention.[43]

Three publications evaluated the feasibility of an educational intervention. In the publication by Gulla et al.,[46] feasibility was measured with a structured interview of nursing home staff consisting mainly of registered nurses and unit managers. Schmidt-Mende et al.[48] analysed two pharmacists' unstructured diaries, including GPs' and nurses' views, and Cadogan et al.[44] conducted a questionnaire survey of GPs in a one-month pilot study in which they implemented an educational online

Table 5
Publications covering implementation outcomes (Proctor et al. 2010) by implementation strategy.

Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
Acceptability							
Cattaruzzi[21] et al., 2018	Medication review	Descriptive pilot study	Clinical pharmacists (7), nurses (4), physicians (31)	Residents (333) of long-term nursing homes (4): Mean age (SD) 84.54 (10.04) Female 72.1% Median number of drugs/patient (range) 8.0 (5.5–10.0)	–	Acceptance rate	Physicians' acceptance rate of drug discrepancies ascertained by clinical pharmacists: 35.5% (309/871) Acceptance rate related to: drug substitutions 91.3% (211/231) dosing regimen modifications 96.4% (53/55) drug withdrawal 36.7% (41/112) drug introduction 57.1% (4/7)
Foubert[22] et al., 2019a	Medication review	Descriptive study	Pharmacists (21), GPs (44)	Community-dwelling patients (75) of community pharmacies (12): Mean age (SD) 78.3 (5.4) Female 61.3% Median number of chronic medications (range) 11 (8–13)	–	Acceptance rate Questionnaire for GPs	GPs' acceptance of pharmacists' recommendations: Recommendations accepted: 70 (66.9%) patients Implementation of pharmacists' recommendations at 3-months follow-up: 60 (42.9%) patients. Main reasons for not implementing accepted recommendations were patient refusal and postponement of the intervention.
Foubert[23] et al., 2019b	Medication review	Descriptive study	GPs (18)	Resident (50) of a nursing home (1): Mean age (SD) 85.7 (5.7) Female 78.0% Median number of chronic medications (range) 9 (7–11)	–	Acceptance rate Questionnaire for GPs	156 relevant pharmacists' recommendations for 49 patients 70 (44.9%) accepted by physician for 34 patients 42 (26.9%) recommendations fully implemented for 20 patients Reasons for not accepting: GP perceives medication as necessary or beneficial: 38 (44.2%) GP perceives the recommendation to be of inferior priority: 19 (22.1%) Previous bad experiences with stopping: 12 (14.0%) Lack of suitable alternative or unwillingness to try alternatives: 9 (10.5%) Another physician started the medication and the GP did not want to interfere: 6 (7.0%) GP perceives that the resident will refuse the recommendation: 2 (2.3%)
Verrue[25] et al., 2012	Medication review	Descriptive study (case-control study for effectiveness)	Clinical pharmacists (NA), GPs (28)	Nursing home (1) residents (69) Mean age (SD) 86.0 (6.7)	Another nursing home receiving usual care (79): Mean age (SD) 79.9 (9.2) Female 65.8%	Acceptance rate Questionnaire for GPs	Recommendations made by the pharmacist (n = 170) accepted by GPs': Completely accepted 40.6%:

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Table 5 (*continued*)

Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
				Female 75.4% Median number of chronic drugs (range) 7 (1–16)	Number of chronic drugs, median (range) 6 (1–19)		Partially accepted 28.8% Rejected 24.1% 111 of the 323 (34.4%) recommendations were implemented 11/28 (39.3%) of the GPs returned questionnaire to evaluate the study and opinion about a monthly medication review: 2/11 reported that recommendations were too theoretical. 1/11 found the recommendations very useful to stay alert. Physicians tended to be in favour of a monthly audit of the medication use performed by a clinical pharmacist.
Chowdhury[29] et al., 2018	Multidisciplinary interventions	Descriptive study (Repeated cross-sectional quality improvement project)	Pharmacist (1), Health care team (geriatrician, nursing staff, case manager, volunteers and management) (NA)	Hospital patients (588) of one general medicine floor: Mean age (SD) 81.2 (7.2) Male 45.1% White race 79.8%	–	Acceptance rate	Acceptance rate by the primary health-care team for all pharmacy recommendations: pre 87% vs post 85%, IRR 0.98: 95% CI: 0.93–1.03
Mekdad[35] et al., 2019	Multidisciplinary interventions	Descriptive study	Geriatric pharmacist, physicians (NA)	Patients aged $\geq$ 65 (375) of one Geriatric Cardiac Clinic: Mean age (SD) 72 (6.2) Male 52%	–	Acceptance rate Questionnaire for physicians	After medication review recommendation were made for 90 (25%) patients, and the managing team accepted them for 80 (89%) patients. Main reason for rejection of medication was that it was prescribed from another centre.
O'Sullivan[39] et al., 2014	Computerized systems	Descriptive study	Pharmacist (1), physicians responsible for patient care in A&E (NA)	Patients (361) admitted through one A&E department: Median age (range) 77 (71–83) Female 50.1% Median number of prescribed medications (range) 9 (6–12)	–	Acceptance rate	548 (54.8%) of the interventions were accepted by the physicians with primary responsibility for patient care.
van der Meer[43] et al., 2018	Computerized systems	Descriptive study	At each pharmacy 1 pharmacist (47), GPs (NA)	Patients (305) of community pharmacies (47): Mean age (SD) 76.5 (8.0) Female 64.0% Number of anticholinergic/ sedative medications, mean (SD) 5.8 (2.1)	–	Acceptance rate	Recommendations proposed in total: 351, of which 148 (48.5%) were accepted by the GP.

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Table 5 (*continued*)

Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
Franchi[45] et al., 2014	Educational intervention	Descriptive study (also Cluster randomized single-blind controlled study)	Clinicians (intervention: 54, control group: 22)	Patients (41) of two geriatric and internal medicine hospital wards: Mean age (SD) 82.8 (5.59) Females 48.78%	The e-learning program for the two control wards consisted only of the basic notions of pharmacology (40 patients): Mean age (SD) 81.58 (5.00) Females 32.50% Number of diagnoses, mean (SD) 6.45 (2.48)	Questionnaire for clinicians	Intervention was well accepted by all participating clinicians, who positively judged the specific contents, methodology applied, clinical relevance and utility of the information for changing clinical practice and tools for evaluation of the appropriateness of drug prescribing (mean score of 3 points on a scale of 5 points: 0 = useless; 5 = most useful) 49/54 (90%) clinicians of the intervention group and 20/22 (91%) in the control group completed their e-learning course. The e-learning programme was completed within a median of 15 days. Time spent by clinicians in the intervention group was 5 h and in the control group 1 h.
Adoption							
Andrew[28] et al., 2018	Multidisciplinary interventions	Observational study	(NA)	Post-CBD patients (370) of long-term care facilities (10): Mean age (SD): 82.1 (12.4) Female 67.6% Dementia: 72,8% Length of stay, months (SD) 32.2 (1.7)	Pre-CBD patients (159): Mean age (SD) 85.7 (10.7) Female 71.7% Dementia: 55.9% Length of stay, months (SD) 71.3 (3.6)	Polypharmacy, PIM rate	Residents taking >10 medications: Pre-CBD 138 (86.6%) vs post-CBD 294 (79.5%), p = 0.046. Residents using potentially inappropriate medication: Pre-CBD 137 (86.2%) vs post-CBD 300 (81.1%), p = 0.16.
Clyne[30] et al., 2016	Multidisciplinary interventions	Descriptive study (process evaluation)	GPs (Intervention: 7, Control: 10)	Patients (11) of primary care general practices (21)	–	Interviews and thematic analysis	8/11 (73%) GPs in the intervention group conducted medication reviews with the participating patients present using web-based pharmaceutical treatment algorithms as outlined in the academic detailing, 2/11 (18%) GPs conducted the reviews using the web-based pharmaceutical treatment algorithms in the absence of the patients and one (9%) GP did not complete any medication reviews. 86/99 (87%) reviews were conducted: 10 (10%) were not conducted as one GP completed no reviews and 3 (3%) were not conducted as the patient was deceased or withdrew. 114 PIP were assessed. 44/114

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Table 5 (*continued*)

Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							(39%) prescriptions were not altered, for reasons including the prescription being initiated in hospital, patient preference, and lack of available alternatives. 8/10 (80%) GPs in the control group reported that they did very little with the feedback letter provided to them. 2 GPs (20%) reported that the simple feedback prompted them to change medications.
Cossette[31] et al., 2016	Multidisciplinary interventions	Observational study (Cohort with interrupted time series)	Pharmacists with expertise in geriatrics (NA), clinicians (NA)	Hospital patients (8,622): Mean age (SD) 83.3 (5.9) Female 54.5% Median length of stay, days 7 7.6% died during the study	Pre-implementation and individuals aged 18 to 64 admitted to CHUS Characteristics (NA)	Patient-days with at least one PIM	At least one PIM was prescribed on 28,776 (19.8%) of the 145,061 patient-days (One PIM 17.1%, two PIMs 2.4% and three or more 0.4%). PIM use at start of observation: 21.89% (20.17–23.60), $p < 0.001$ Pre-intervention trend, per month: 0.11% (−0.31–0.09), $p = 0.31$ Change in rate immediately after intervention: 2.55% (−5.58–0.47), $p = 0.12$ Change in trend after intervention, per month: 0.11% (−0.40–0.62), $p = 0.68$ Targeted clinician groups mentioned barriers to changing prescribing practices: Prehospital chronic use of PIMs Lack of knowledge of safer pharmacological and non-pharmacological alternatives
Keith[33] et al., 2013	Multidisciplinary interventions	Observational study	GPs Parma (303), Emilia-Romagna (325)	Older patients served by the Parma LHA who had at least one outpatient prescription (78,482): Mean age (SD) 75.6 (7.3), Female 59.2% Prescriptions per patient, mean (SD) 4.1 (2.7)	The neighbouring Reggio Emilia Local health authority (LHA) (81,597): Mean age (SD) 75.4 (7.2) Female 58.2% Prescriptions per patient, mean (SD) 4.0 (2.5)	PIM incidence	Quarterly incidence rates of PIMs reduced 31.4% in Parma LHA from baseline in 2007 (7.8%) to Q4 in 2009 (5.3%). Compared to Reggio Emilia LHA from baseline to 2009 Q4: Parma LHA 31.4% vs. Reggio Emilia LHA 21.6%, $p < 0.001$
Moss[36] et al., 2016	Multidisciplinary interventions	Observational study (mixed methods)	CPS (approximately 30, physicians (NA)	Patients aged >65 discharged from the Durham VAMC (23,168) Characteristics (NA)	–	Monthly PIM rates	21,526 medications prescribed to 23,168 adults, of which 2,684 identified as PIMS. Monthly PIM rates varied from 7.0% January 2012 to 9.3% January 2013 pre-

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							implementation and from 7.9% in February 2013 to 4.9% in November 2014 during the QI initiative. Semi-structured interviews with the CPS involved in the project and the site principal investigator for insight into CPS roles. Authors state that the findings reinforce the role of CPS and the importance of their contribution to QI projects.
Moss[37] et al., 2019	Multidisciplinary interventions	Observational study (Process evaluation)	Internal medicine residents (50 completed pre-intervention questionnaire and 29 completed the post-intervention questionnaire)	Patients aged >65 years discharged from the Durham VAMC EM (3,162) Characteristics (NA)	Patients of physician residents who did not receive the educational intervention (2,500) Characteristics (NA)	PIM rate	The resident cohort who received the educational intervention were less likely to prescribe a PIM when compared to the untrained resident cohort (rate ratio = 0.73, 95% CI = 0.632–0.850, $p < 0.0001$).
Rieckert[40] et al., 2018	Computerized systems	Qualitative study	GPs (21)	–	–	Semi-structured interviews and thematic analysis	Most GPs reported having changed medication due to the recommendations, but some GPs reported that they were not able to follow them. GPs felt that the majority of patients taking part in the trial reacted in an open-minded and cooperative way towards recommended changes in medication. Patients were sometimes apprehensive about negative effects when changing long-term. Prescriber factors: Sometimes GPs did not follow recommendations, as they feared that changing medication could be complex. If they had been prescribing the medication for years, they lacked motivation to reconsider it or did not want to diverge too far from a standard of therapy (guidelines). Patient factors: GPs felt that the willingness to change medication depended on the actual medication and priorities of the patient. External factors GPs were reluctant to discontinue medication prescribed by other medical specialists without contacting them.

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							Infrastructural factors A further barrier was that the CMR was sometimes conducted without the patient being present in the practice (e.g. outside of practice hours) and thus medication changes resulting from the CMR could have been delayed or even forgotten.
Rieckert[41] et al., 2019	Computerized systems	Descriptive study	GPs (160)	–	–	Questionnaire for GPs	18% of the GPs conducted the CMR and additional medication review for all study patients. 60% conducted the CMRs for their study patients as required by the study protocol of the RCT 18% for only some of the study patients. 4% did not answer the question.
Rognstad[47] et al., 2013	Educational intervention	cRCT	Average of 7.5 GPs/General practices Continuing medical education group	GPs listed patients aged ≥70 years (pre 46,737 post 45,310) of general practices Continuing medical education group (41) Characteristics (NA)	Patient (pre 35,073 post 35,211) assigned to control group (41) (Another educational intervention targeting antibiotic prescribing practice for respiratory tract infections) Characteristics (NA)	Total PIPs per 100 patients	Intervention group Control group Changes due to the intervention n = 250 GPs n = 199 GPs Absolute change Relative change Baseline % Change % Baseline % Change % % (95% CI) % (95% CI) 27.3–4.9 25.8–1.6 –3.3 –12.1 (5.6 to −0.9) (−16.8 to–6.9)
Bachyrycz[49] et al., 2012	Other interventions	Descriptive study	Practitioners (12,000)	–	–	Guideline use	Web-based guideline was viewed an average of 163 times per month. Additionally, the alternative treatment recommendations and strategies section of the website had been viewed an average of 407 times per month. Barriers identified in the guideline development and dissemination process: Knowledge variances, willingness to change, and differences in opinion and many health care provider audiences were not familiar with the Beers' criteria.
Appropriateness							
Clyne[30] et al., 2016	Multidisciplinary interventions	Descriptive study (process evaluation)	GPs (Intervention: 7, Control: 10)	Patients (11) of primary care general practices (21)	–	Interviews and thematic analysis	All GPs described conducting the reviews with the patients positively. The intervention website and treatment algorithms were considered simple and easy to engage with by all GPs. 8/10 of GPs reported that patients were overall 'very

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							receptive' to the review process. All patients interviewed reported that medication reviews were a good idea. Regardless of whether or not changes were made to their medication, patients were receptive to medication review.
Vandenberg[38] et al., 2018	Multidisciplinary interventions	Descriptive study and post-intervention telephone interviews	Providers (physicians 15, advanced practice providers 5)	>65 years, rural area veterans (>7,000) of community-based outpatient clinics (4), 21 telephone interviews	–	A telephone interview for PCPs	Satisfaction with the IMPROVE intervention after the implementation: 10 PCPs specifically recalled reviewing their individualized feedback forms and finding them helpful in their prescribing practice. All PCPs indicated that the education session was useful. Several requested that education on geriatric prescribing practices be refreshed annually. Twelve indicated that they preferred paper tools (e.g., Beers pocket cards).
Rieckert[41] et al., 2019	Computerized systems	Descriptive study	GPs (160)	–	–	Questionnaire for GPs	GPs who discontinued medications reported having to restart a discontinued medication: 20% never, 35% rarely, 37% occasionally, and 8% often. 66% discussed the recommendations with their patients, 30% discussed the recommendations to some extent, and 4% did not discuss the recommendations at all. Attitude toward the CMR: 82% judged the CMR to be informative, 70% easy to understand, 69% useful and 62% clear. 85% of the GPs agreed or strongly agreed that the recommendations increased their awareness 46% of the GPs agreed or strongly agreed that the PRIMA-eDS tool serves to improve doctor-patient communication 33% agreed or strongly agreed that it helps to better communication with other specialists.
Vandenberg[42] et al., 2017	Computerized systems	Descriptive study	Physicians (intervention 10, comparison 10)	–	–		Use All EQUiPPED providers were

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
						Structured interviews of providers	aware of the existence of the geriatric order sets and had viewed them. Providers varied in their use of geriatric order sets, ranging from occasional use to consultation to adoption. Non-users either felt their autonomy was threatened or that pre-existing prescribing tools were adequate. Usefulness Facilitators: Safety, Efficiency, Information, Training Barriers: Autonomy, Comfort Usability Facilitators: Location, Categorical organization, prepopulated fields Barriers: Learning curve
Cadogan[44] et al., 2018	Educational intervention	Descriptive pilot study	GPs (3)	Patients (10) of general practices (2): Mean age 73.1 Female 60% Median medicines 6	–	Questionnaire for GPs	Each GP reported watching the online video at least once prior to the first patient consultation that was scheduled as part of the study. GPs reported that the videos would improve their performance of medication reviews with older patients. GPs reported mixed views about whether videos would help them to review older patients' medications more quickly in daily practice (1 strongly disagree, 1 disagree, 1 agree). All GPs stated that they would recommend the video to a colleague. All GPs reported making changes to the patients' prescriptions. All GPs reported that having protected time would encourage them to perform medication reviews.
Schmidt-Mende[48] et al., 2018	Educational intervention	Qualitative study	Physicians (median 8.7/practice), nurses (median 7.0/practice), educating pharmacist (2)	–	–	Narrative and unstructured diaries written by two pharmacists	The diaries included GPs' and nurses' views on medication reviews, and they were grouped into five themes. Theme 1. Older patients often had complex problems, pharmacotherapy was a complex subject and primary care had a complex role in the health care system. Theme 2. The separation into

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							'basic' and 'complex' medication reviews was arbitrary and did not correspond to clinical experience. Theme 3. GPs and nurses may identify numerous 'real-world' problems when trying to implement new guidelines. There was variation regarding the motivation to collaborate and their experiences regarding their collaboration. Difficulties with the documentation and the registration of medication reviews. The forms to fill in during a medication review were too complex, and it was unclear how to code correctly. Theme 4. Experiences varied in relation to the usefulness of standardized questionnaires screening for side effects, it was generally considered that they caused more work and are difficult to interpret. Theme 5. External steering as represented by the guidelines caused frustration and even passiveness, as they challenged GPs' capacity to correctly evaluate a patient's medical complaints. GPs and nurses perceived that financial incentives forced them to perform medication reviews when they were actually not indicated from a medical point of view.
Feasibility							
Foubert[23] et al., 2019b	Medication review	Descriptive study	GPs (18)	Residents (50) of a nursing home (1): Mean age (SD) 85.7 (5.7) Female 78.0% Median number of chronic medications (range) 9 (7–11)	–	Questionnaire for GPs	Reasons for not implementing accepted recommendations (70 (44.9%) of 156 recommendations accepted, 42 (26.9%) of accepted implemented): Resident refused treatment modification: 6 (18.8) Treatment modification was postponed: 5 (15.6) GP changed their mind after the pharmacist-GP meeting: 3 (9.4) No reason provided to the head nurses: 18 (56.3)
Wilchesky[26] et al., 2018	Medication review	Descriptive study (quasi-experimental)	GPs (5), clinical pharmacists (4), heads of NH care units (6) and staff nurses (19)	Residents with a diagnosis of severe dementia (44) of	–	Post-intervention knowledge exchange session and open-	All respondents found the MRG tool useful or very useful. More than half of respondents

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
				nursing homes (3): Mean age (SD): 86.9 (6.9) Female 70.5% Mean medication administration problems (scale of 0–13 (SD)) 0.23 (0.86)		ended questions to health professionals.	did not notice an increase in their workload. Two thirds of respondents mentioned multiprofessional relations as very important and one third indicated that information exchange had been clear and rigorous. Barriers: Workload Difficulties in communication between shifts Staff turnover GPs and pharmacists often off-site Discontinuation of antipsychotic agents was regarded difficult
Clyne[30] et al., 2016	Multidisciplinary interventions	Descriptive study (process evaluation)	GPs (Intervention: 7, Control: 10)	Patients (11) of primary care general practices (21)	–	Interviews and thematic analysis	Process evaluation identified relative advantage, compatibility and observability of OPTI-SCRIPT, but in the GPs' opinion current workloads made medication reviews for all older patients unfeasible due to time constraints. Workload, time to conduct the medication review and reimbursement mechanisms were recognized as organizational barriers to adoption. Simplicity, patient receptivity and positive aspiration were recognized as facilitators of implementation.
Moss[37] et al., 2019	Multidisciplinary interventions	Observational study (Process evaluation)	Internal medicine residents (50 completed pre-questionnaire and 29 completed the post-questionnaire)	Patients aged >65 years discharged from Durham VAMC EM (3,162)	Patients of physician residents who did not receive the educational intervention (2,500)	Questionnaire for internal medicine residents	I routinely consider my patients age when prescribing medication in ED: Pre 94% vs 100% (p = 0.1106) agreed. I have confidence in my ability to: prescribe appropriate medication for older adults: pre 90% vs post 100% (p = 0.0251) agreed. identify drug-disease interactions in older adults pre 80% vs 100% post (p = 0.0053) agreed. identify adverse drug reactions in older adults pre 86% vs post 97% (p = 0.0692) agreed. I routinely consult Beers Criteria when prescribing medication to older adults in the ED: pre 14%

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							vs post 66% ($p < 0.0001$) agreed.
Rieckert[40] et al., 2018	Computerized systems	Qualitative study	GPs (21)	–	–	Semi-structured interviews and thematic analysis	The estimated time needed to read the CMR varied (5–20 min). Retrieving additional information provided by the tool was perceived as being too time-consuming. Some GPs mentioned that they hoped for a learning effect that would shorten expenditure of time in the future. Barriers: Time, the required internet access, and possible costs (without being reimbursed). Possible technical problems; ensuring data security
Rieckert[41] et al., 2019	Computerized systems	Descriptive study	GPs (160)	–	–	Questionnaire for GPs	Barriers to implement recommendations: Perceived necessity of the medication (69%) Prior trial of suggested alternative medications (54%) Another specialist being involved in prescribing the medication (35%) Future use: Remuneration is important only for 20% of GPs. 65% would use the CMR if it was part of the electronic health record 25% would possibly 10% would not use the PRIMA-eDS tool. 160 of 176 questionnaires were returned from GPs
van der Meer[43] et al., 2018	Computerized systems	Descriptive study	At each pharmacy 1 pharmacist (47), GPs (NA)	Patients (305) of community pharmacies (47): Mean age (SD) 76.5 (8.0) Female 64.0% Number of anticholinergic/ sedative medications, mean (SD) 5.8 (2.1)	–	Questionnaire for pharmacists	43 (91.5%) pharmacists were satisfied with the IT-based intervention 41 (87.2%) pharmacists found it meaningful 41 (87.2%) pharmacists found it practical 46 (97.9%) pharmacists found it clear 44 pharmacists (93.6%) found it educational 33 (70.2%) pharmacists wanted to keep using the intervention in the future.
Cadogan[44] et al., 2018	Educational intervention	Descriptive pilot study	GPs (3)	Patients (10) of general practices (2): Mean age 73.1	–	Questionnaire for GPs	Each GP reported watching the online video at least once prior to the first patient consultation

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
				Female 60% Median medicines 6			that was scheduled as part of the study. GPs reported that the videos would improve their performance of medication reviews with older patients. GPs reported mixed views about whether the videos would help them review older patients' medications more quickly in daily practice (1 strongly disagree, 1 disagree, 1 agree). All GPs stated that they would recommend the video to a colleague. All GPs reported making changes to patients' prescriptions. All GPs reported that having protected time would encourage them to perform medication reviews.
Schmidt-Mende[48] et al., 2018	Educational intervention	Qualitative study	Physicians (median 8.7/practice), nurses (median 7.0/practice), educating pharmacist (2)	–	–	Narrative and unstructured diaries written by two pharmacists	The diaries included GPs' and nurses' views on medication reviews, and they were grouped into five themes. Theme 1. Older patients often had complex problems, pharmacotherapy was a complex subject and primary care had a complex role in the health care system. Theme 2. The separation into 'basic' and 'complex' medication reviews was arbitrary and did not correspond to clinical experience. Theme 3. GPs and nurses may identify numerous 'real-world' problems when trying to implement new guidelines. There was variation regarding the motivation to collaborate and their experiences regarding their collaboration. Difficulties with the documentation and the registration of medication reviews. The forms to fill in during a medication review were too complex, and it was unclear how to code correctly. Theme 4. Experiences varied in relation to the usefulness of standardized questionnaires screening for side effects, it was generally considered that they

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							caused more work and are difficult to interpret. Theme 5. External steering as represented by the guidelines caused frustration and even passiveness, as they challenged GPs' capacity to correctly evaluate a patient's medical complaints. GPs and nurses perceived that financial incentives forced them to perform medication reviews when they were actually not indicated from a medical point of view.
Gulla[46] et al., 2019	Educational intervention	Descriptive study	Nursing staff (105, including 7 physicians)	Residents (297) of nursing home units (36): Mean age (SD) 87 (7.7) Female 73% Mean registered diagnoses (SD) 4(3.3) Mean number of drugs/day (SD) 7.6 (3.8) Number of on demand prescriptions (SD) 3.4 (2.3)	–	Structured questions to nursing staff	92% of the patients had undergone a medication review, changes in the patients' health were documented for 77% of the patients, 30% of the patients were put back on a deprescribed drug. Barriers: New and difficult clinical instruments Lack of competence Practical challenges with changing drug regimes Poor knowledge about electronic patient records Lack of time Ethical dilemmas Promoters: Engagement Arena for learning Introducing a colleague to discuss difficult decisions with The intervention was perceived as important and relevant Improved communication Pleased relatives
Fidelity							
–							
Implementation cost							
Gillespie[32] et al., 2017	Multidisciplinary interventions	Cost-effectiveness analysis (cRCT)	GPs (NA), pharmacists (NA)	Patients (99) of primary care practices (11): Mean age (SD): 77.1 (4.9) Male 55.6% Repeat medications, mean (SD) 10.2 (4.5)	Patients (97) of usual primary care practices in addition to a one-off simple patient-level PIPs feedback (10): Mean age (SD): 76.4 (4.8) Male 51.5% Repeat medications, mean (SD) 9.5 (4.1)	ICER, (QALY & implementation cost)	Incremental cost-effectiveness ratios (ICERs): €30,535 (95% CI, −334,846–289,498) per QALY gained €1269 (95% CI, −1400–6302) per PIP avoided. The probability of the implementation strategy being cost-effective compared to usual primary care was at least 0.845 at threshold values of €2500 per

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Publication	Implementation strategy	Study design	Healthcare professionals (n)	Patients	Patient control	Implementation process measure	Results of the process measure
							PIP avoided and higher. The probability of the intervention being cost-effective was 0.602 at a threshold value of €45,000 per QALY gained.
Penetration							
Ödesjö[27] et al., 2017	Medication review	Observational study (registry cohort)	Providers (196)	Primary care patients (144,222) ≥1 appointment in same primary care unit during year 2009: Mean age (SD) 81.8 (5.1) Female 59.7%	No control group	Proportion (%) of patients with registered medication review	Year 2009 2010 2011 2012 2013 3.2 27.4 40.5 46.2 44.1
Sustainability							
Kempen[24] et al., 2019	Medication review	Qualitative study (Case study)	Physicians (6), pharmacists (3), nurse (1)	–	–	Semi-structured interviews of healthcare professionals	Interviewees regarded politics and media as important promoters and barriers for implementation. The focus of the national government on improving care for older patients, including the role of quality indicators, legislation and financial support, and involvement of the public and media supported the implementation. Lack of political focus, monitoring and evaluation were regarded as barriers. Patient focus, multiprofessional collaboration and appropriate resources are important factors for developing an innovative culture and changing roles. Education for healthcare professionals and ICT developments were also facilitating factors.
Lopatto[34] et al., 2014	Multidisciplinary interventions	Observational study (proof-of-concept registry)	GPs (299)	Older patients served by the Parma LHA (111,282): Mean age (SD) 75.29 (8 34) Female 57.9%	Comparable data from the neighbouring Reggio-Emilia LHA (population similar to the Parma LHA (Keith et al. 2013[33]))	PIP incidence (patient received at least one PIP medication in a given quarter)	PIP exposure incidence rates decreased during the intervention (from 7.1% to 4.9%), and in the post-intervention phase (from 4.9% to 4.3%). Newly exposed PIP incidence rate also decreased during the intervention (from 4.7% to 3.1%) and post-intervention phase (from 3.1% to 2.7%).

GP, general practitioner; SD, standard deviation; NA, not available; CBD, Care by Design model; CHUS, Centre Hospitalier Universitaire de Sherbrooke; PIM, potentially inappropriate medication; PIP, potentially inappropriate prescribing; CPS, clinical pharmacy specialists; MRG tool, medication review guidance; CMR, comprehensive medication review; ICT, information and communications technology; QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; PCP, primary care providers; ED, emergency department; IRR, incidence rate ratio; CI, confidence interval; IT, information technology; DBI, drug burden index; A&E, accident & emergency; PPO, potential prescribing omission; KE, knowledge exchange.

video.

Implementation cost

Only one publication evaluated implementation cost. The multidisciplinary intervention by Gillespie et al.[32] was conceptualized as a cost-effectiveness analysis of the OPTI-SCRIPT implementation strategy cRCT, which was already observed to be effective in reducing PIP in the short term.[50] In the cost-effectiveness analysis the multidisciplinary intervention's costs and effectiveness were compared to care as usual. Analysis included the cost of implementing the intervention in clinical practice for the intervention arm. Implementation cost included the pharmacists' and GPs' time input relating to the review and identification of PIPs, educational materials and consumables, and travel expenses.[32]

Penetration

The observational study by Ödesjö et al.[27] evaluated the penetration of a mandatory medication review from the viewpoint of a health authority. Their aim was to determine whether pay for performance linked to medication review coding was associated with an increase in the volume of medication reviews. There was a lower and upper limit for financial compensation. At the end of the study period, no compensation was granted if the proportion of patients with a medication review code was less than 30%, and maximum compensation was granted if the proportion was 60% or more.

Sustainability

Two publications considered the sustainability of mandatory implementation strategies. One was a qualitative process evaluation of a medication review with no specific timeframe reported.[24] The aim of the publication was to identify factors of successful implementation sustainability based on semi-structured interviews of different health care professionals. Lopatto et al.[34] reported a 6-year observational registry study on the implementation of a national QI project.[34] They evaluated the change in PIP rates after the implementation strategy was removed from the Parma LHA region and used in the neighbouring Reggio-Emilia LHA as a control group.

Discussion

Meaning of the scoping review findings

We identified 29 publications that evaluated the process of implementation strategies for reducing PIM prescribing in the older population; although we searched data from the early 2000s, all included publications were from the 2010s. All implementation outcomes categorized by the framework of Proctor et al.[1] were covered except fidelity. The framework is comprehensive and general, and therefore suitable for a scoping review. Most of the process evaluations took place at the initial stages of the process (acceptability, adoption, appropriateness, and feasibility), and they were often examined along with short-term (<12 months) effectiveness. Acceptability was evaluated in nine publications, adoption and feasibility in ten publications, and appropriateness in six publications. Evaluation of sustainability or implementation costs was rare. The absence of fidelity in this review is undestandable. In medication prescribing, the risk of bias in the way it is performed is smaller than, for example, therapies. Nevertheless, measuring fidelity would provide valuable information on participant responsiveness, strategies to facilitate implementation, and quality of delivery.

The short research history of implementation process evaluation seems to be reflected in the heterogeneity of implementation process conceptualization. In half of the publications (15/29) the concepts used were in concordance with the framework of Proctor et al.,[1] but there were also differences. Acceptability and adoption, and appropriateness and feasibility are very closely connected in the framework, and this difficulty in specification could be seen in the indeterminate use of these concepts. This is also an indication of the complexity of implementation process evaluation.[14,51]

The distinction between acceptability and adoption studies can be problematic. According to Santos et al.[8] there is a need for information on physicians' acceptance of medication reviews, which may have led to the wider range of medication review evaluations of acceptability. On the other hand, there were no adoption evaluations in the medication review category, and it is possible that these implementation outcomes were not separated conceptually from each other. In addition, when evaluating adoption, it was common to use only the term implementation without specifying which part of the process was studied. Appropriateness and feasibility displayed the most differences in conceptualization, with the publication authors using five different concepts for each of these implementation outcomes. Based on the RE-AIM framework, they both are categorized into 'adoption'.[52] According to Proctor et al.,[1] appropriateness is regarded as the usefulness and usability of the implementation strategy, and feasibility is used as a potential explanation of implementation strategy success or failure in a given setting or organization. Implementation cost and penetration, which were represented in single publications, also differed in their conceptualization compared to the Proctor et al. framework.[1] Implementation cost is an independent implementation outcome in the framework of Proctor et al.,[1] but the RE-AIM framework does not identify implementation cost as an independent factor, which is a limitation of the framework.[53] The conceptualization of sustainability was similar to the framework,[1] but only two studies evaluated it. In addition, sustainability and adoption have the same measures as effectiveness evaluation, which also complicates the conceptualization.

The effectiveness of multidisciplinary intervention in PIM prescribing has been studied widely, and in this review multifaceted interventions were the most researched implementation strategy. Other interventions that also include patient education were represented in only one publication. This was due to our focus on decision support and exclusion of patient education. It seems that implementation process evaluations of the different strategies focus on different implementation process outcomes: Medication review was more common in acceptability evaluations, multidisciplinary interventions in adoption evaluations, and computerized systems and educational interventions in feasibility evaluations. Overall, long-term implementation process evaluation and implementation cost evaluation are needed in all the implementation strategy categories. This scoping review can help future research to identify knowledge gaps in different implementation strategies process evaluation. However, we focused on how process evaluation is studied, and it is not possible to state on the basis of this review if there are differences in the success of the implementation strategy categories.

In the initial stages of the implementation process, implementation strategy categories were mostly non-mandatory strategies. Unfortunately, the organizer of the implementation strategy was not always reported in the included publications. We were therefore required to determine the status of the strategy based on the information presented in the articles. If the organizer was stated unclearly, we assumed that the implementation strategy was organized by the research group. The long-term studies evaluated mandatory strategies,[24,27,34] which may be a consequence of funding, as small research groups might not have sufficient funding to study the implementation process over the long term. This is familiar in implementation strategy effectiveness studies, where evidence of long-term effectiveness is often missing.[8] Also, wider implementation over organizational boundaries might not be in the interest of the research groups.

As stated in the literature, the implementation process can be evaluated with different outcomes and different study designs. Qualitative designs are mainly not as representative as quantitative designs, but at the same time, qualitative studies can produce more detailed information about the implementation process.[9,12,51] In this review, study designs were mainly descriptive, but there were also some observational

studies, qualitative studies and cRCTs. Use of a control group was rare and was more common in studies where adoption or sustainability was measured using patient outcomes. Also, the sample sizes were mainly small, and with respect to health care professionals they were sometimes completely missing. Descriptive study designs are justified when the aim is not to evaluate the effectiveness of the implementation process. Process evaluation usually requires a combination of quantitative and qualitative methods but, according to Moore et al.,[51] their use may vary according to the stage of the evaluation process.

In this review a variety of different implementation strategies was identified, and these also took place in different countries and health care environments. PIM use depends considerably on the context and criteria used, which complicates the comparison of studies. The same problem also applies to reviews evaluating the effectiveness of implementation strategies.[8] Country-specific details of medications should always be considered when interpreting the results of studies examining PIM use. PIM criteria differ, some are broader, others more limited. In addition, their purpose of use varies, some are substance-based, others disease-based. Especially when PIM prescribing is used as the outcome, it is essential to note these differences.[54] For example, O'Sullivan et al.[39] obtained different results when using different criteria in their study. It is also important for guideline developers to consider the nature of guidelines as there is a need for recommendations that are understandable and useable for all target groups.[55]

Organizational culture and management have an important role in successful implementation.[56,57] In most of the included publications of this review, the viewpoint was health care professionals. The process was evaluated from the patients' point of view in a few publications, but the management viewpoint on implementation was almost entirely lacking. Only the publication by Wilchesky et al.[26] included heads of care units in their evaluation of health professionals' opinions of feasibility. As managers can positively or negatively impact change in organizations, they play a crucial role in facilitating a positive climate for innovation. It has been noticed in the earlier literature that the role of leadership in implementation of clinical guidelines is rarely empirically examined, although it is often discussed.[57]

Conceptualization should be transparent and unified in order to clarify the research area, as different implementation strategies and process evaluations consist of several stages and levels.[9,58] Therefore, it would be helpful if process evaluations of similar interventions are built on each other's findings using comparable methods, where possible, to enable meaningful comparisons across studies.[51] In this review, we clarified the concepts of implementation process evaluation to facilitate future analyses of the relation between process evaluation and implementation strategy effectiveness.

Strengths and limitations

This scoping review is the first of its type to examine the literature on process evaluation of implementation strategies in PIM prescribing in the older population. We applied a broad search strategy, which produced a broad search result. Therefore, we were compelled to limit the search partly by the title (APPENDIX A), which may have affected the search results. Even though the keywords used were broad, they may exclude some potential publications. Unified concepts in implementation research on PIM prescribing have not yet been established, and there may be publications that have not been initially identified as implementation process evaluations. Based on the abstracts of the included publications, we excluded short-term effectiveness studies. In addition, this review excluded patient education interventions, as the focus of the review was on decision support for health care professionals.

In addition, the categorization of the included implementation strategies[8] into medication reviews, multidisciplinary interventions, educational interventions, computerized systems, and other interventions was not always self-evident. The categorization of medication reviews was especially challenging. Multidisciplinary interventions, educational interventions and computerized systems are all based on medication reviews. If these other actions were not identified in the publication, we categorized it as a medication review. However, for example, education of health care professionals might have been carried out, but not reported in the publication. Ultimately, an up-to-date medication list is always a prerequisite for successful implementation strategies aimed at reducing PIM prescribing, in any circumstances.

Furthermore, we applied the framework of Proctor et al.[1] in grouping the publications according to implementation outcomes. Other less comprehensive frameworks would have given a different scope of publications, as discussed in section 5.1, 'Meaning of the scoping review findings'. As mentioned previously, the authors of the included publications did not always specify which part of the process evaluation they were studying, and the categorization used in this review is based on the information presented in the publications.

This scoping review examined how process evaluation is studied and, therefore, the results of the included publications (presented in Table 5) are not discussed in this article. Moreover, although several publications examined the effectiveness of implementation strategies along with process evaluation, the effectiveness results are not included in this review.

Conclusions

The conceptualization of implementation process evaluation was similar in only half of the publications. This is an indication of the indeterminate use of concepts, and the complexity of implementation process evaluation. Clarifying the conceptualization of implementation process evaluation is important in order to be able to effectively translate research knowledge into practice.

Most of the process evaluations took place in the initial stages of the process. Acceptability was evaluated in nine publications, adoption and feasibility in ten publications, and appropriateness in six publications. Sustainability and implementation costs were seldom evaluated. None of the included publications evaluated fidelity.

Multifaceted interventions were the most studied implementation strategies. Medication review was more common in acceptability evaluations, multidisciplinary interventions in adoption evaluations, and computerized systems and educational interventions in feasibility evaluations. However, it is not possible to state on the basis of this review if there are differences in the success of the implementation strategy categories, and more research is needed

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2021.04.012.

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ARTICLE II

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RESEARCH PAPER

Cost-effectiveness of an educational intervention to reduce potentially inappropriate medication

Mervi Rantsi[1], Kaisu H. Pitkälä[2], Hannu Kautiainen[2], Virva Hyttinen[1], Eila Kankaanpää[1]

[1]Department of Health and Social Management, University of Eastern Finland, Kuopio 70211, Finland
[2]Department of General Practice, University of Helsinki, Helsinki 00014, Finland

Address correspondence to: Mervi Rantsi. Email: mervi.rantsi@uef.fi

Abstract

Background: Educational interventions can reduce potentially inappropriate medication (PIM) use in older people. Their effectiveness has been measured mainly as changes in PIM use. In this economic evaluation, we analyse the impact of an educational intervention in terms of costs and quality-adjusted life years (QALYs).
Methods: The educational intervention consisted of activating and interactive training sessions for nursing staff and consulting physicians, and was compared with treatment as usual (TAU). Participants ($n = 227$) in a cluster randomised trial (cRCT) were residents living permanently in assisted living facilities ($n = 20$ wards). For economic evaluation, participants' healthcare service use costs and costs for the intervention were estimated for a 12 month period. Incremental cost-effectiveness ratios (ICERs) were estimated for QALYs per participant. Cost-effectiveness analysis was conducted from a healthcare perspective. A bootstrapped cost-effectiveness plane and one-way sensitivity analysis were undertaken to analyse the uncertainty surrounding the estimates.
Results: The educational intervention was estimated to be less costly and less effective in terms of QALYs than TAU at the 12 month follow-up [incremental costs –€1,629, confidence interval (CI) –€5,489 to €2,240; incremental effect −0.02, CI –0.06 to 0.02]. The base case ICER was >€80,000/QALY.
Conclusion: The educational intervention was estimated to be less costly and less effective in terms of QALYs compared with TAU, but the results are subject to some uncertainties. Reduction in PIM use or benefits in quality of life did not seem to translate into improvements in QALYs. Our findings emphasise the need for better understanding of the impact of decreasing PIM use on health outcomes.

Keywords: economic evaluation, older people, educational intervention, implementation intervention, potentially inappropriate medication

Key Points

- Educational interventions have been studied mainly in terms of potentially inappropriate medication (PIM) use rather than health outcomes or costs.
- Educational intervention was estimated to be less costly and less effective in terms of quality-adjusted life years (QALYs), compared with usual treatment.
- We found that reduction in PIM use or benefits in terms of quality of life did not seem to translate into improvements in QALYs.
- Although QALYs are commonly used in economic evaluations, they might not be suitable in end-of-life care of frail older people.

Introduction

Medication of older people is defined as potentially inappropriate if the associated risks outweigh the potential benefits [1]. Potentially inappropriate medication (PIM) use is associated with adverse drug events, reduced cognitive and physical functioning, decreased quality of life (QoL), hospitalisation and mortality [2–4], and thus with increased healthcare utilisation and costs [5], and higher medication costs [6, 7]. The prevalence of PIM use in Europe is >20% in community-dwelling older people and 49% in older people living in nursing homes [8, 9], and in the USA the prevalence is even higher [10, 11].

The effectiveness of implementation interventions to reduce PIM use has been widely studied. Implementation interventions are usually categorised into medication review services, multidisciplinary interventions, computerised systems, educational interventions and other interventions [12]. Educational interventions, including sessions for health professionals, distribution of materials and training for patients and caregivers, may reduce PIM use and hospitalisation in older people [12]. Educational interventions with fewer educational sessions and poor physician attendance did not show improvement in prescriptions [13, 14]. It appears that interactive approaches with direct feedback are more effective than the dissemination of written material [15]. However, interventions have been studied more in terms of changes in PIM use rather than health outcomes or costs [12, 16].

Although effectiveness studies abound, economic evaluations of implementation interventions to reduce PIMs of older people are rare. There are generally four types of economic evaluations: cost–benefit analysis, cost-minimization analysis, cost-effectiveness analysis and cost-utility analysis. Cost-effectiveness and cost-utility analysis can support optimal patient care and the choice of efficient implementation interventions by comparing the costs of interventions with their health benefits [17]. Recent literature has recognised the need for economic evidence in implementation science, but there is still scope for the use of high-quality cost-effectiveness analyses [18].

A model-based economic evaluation by Sanyal *et al.* [19] estimated the cost-effectiveness of an educational intervention in discontinuing non-steroidal anti-inflammatory drugs (NSAIDs) in community-dwelling older people. The intervention was dominant, i.e. less costly and more effective in terms of quality-adjusted life years (QALYs) than usual care at 12 month follow-up. To reduce antipsychotic use in persons with dementia living in nursing homes, Ballard *et al*. [20] focused on an intervention that consisted of an antipsychotic review and staff training in person-centred care and social interaction. They found this educational intervention to be economically dominant at the 12 month follow-up: compared with treatment as usual (TAU), it was more effective in terms of QoL and was also cost-effective.

Economic evaluation studies on other implementation interventions to reduce PIM use exist. They concern multidisciplinary interventions and medication reviews [21–24]. The decision concerning cost-effectiveness in these studies has been dependent on the decision-makers' valuation of the specific outcome unit [22], but only short-term (≤12 months) cost-effectiveness has been evaluated. The studies used different outcome measures, but the impact on QALYs received less attention.

In this study, we examine the cost-effectiveness of an educational intervention to reduce PIM use and its impact on QALYs in residents in assisted living facilities compared with TAU. The primary outcomes of this trial have been reported earlier [25].

Method

We conducted a cost-effectiveness analysis from a healthcare perspective based on a cluster randomised controlled trial (cRCT) [25]. This economic evaluation adhered to the Consolidated Health Economic Evaluation Reporting Standards Statement (CHEERS) [26].

Study design

In total, 36 assisted living facility wards in Helsinki, Finland were assessed for possible participation in this cRCT. The level of care in assisted living facilities is comparable with that in nursing homes or long-term hospital care.

Of these 36 assisted living facility wards, seven facilities with 20 wards were selected. The minimum data set [27] was used to determine the case mix of each ward. A total of 20 wards were paired into 10 dyads according to their case mix. The wards in each dyad shared similar resident characteristics. These 20 dyads were then randomised to intervention and control groups during the years 2011 and 2012 [28]. The pairs of wards were randomised rather than the participants, in order to prevent contamination. Dyads were randomised using a computerised random number generator.

Intervention

The intervention consisted of two 4 h training sessions organised by a research geriatrician for nursing staff and consulting physicians. Training sessions were based on a constructive learning theory [29, 30]. The aim of the training was to enable nurses to recognise different PIMs and adverse drug events. PIMs were any of the following: Beers criteria medications [1], anticholinergic medications, use of multiple psychotropic medications, NSAIDs and proton pump inhibitors.

The first session was lecture based, and the participants were encouraged to discuss medication-related problems experienced in their residents. The lecture introduced the list of inappropriate medications and suitable alternatives, drug–drug interactions and medication use for residents with renal impairment. The second session was based on participants' own case studies. The nurses participated in

discussions about medication-related problems by presenting and discussing actual cases from their own wards. A list of inappropriate medications was provided for all nurses in the intervention wards. Nurses were invited to identify medication-related problems and inform the consulting physician who was responsible for changes in medications.

The training was especially targeted to those 2–3 registered nurses in the intervention wards who were responsible for residents' medication. In seven intervention wards, those nurses participated in both sessions. There were two wards in which the nurses did not participate in the first session but participated in the second session. In one ward, the nurses did not participate in either of the sessions and they received tailored individual training. In addition, one geriatrician and one primary care physician were able to participate in one session, and they received tailored individual training.

Participants

Nurses, who were not aware which of the wards were randomised to intervention and control groups, recruited the residents to participate in the study. The residents were included if they were aged >65, living permanently in the assisted living facilities, Finnish speaking, using at least one medication, life expectancy >6 months and able to provide written informed consent (or had a proxy who was able to do so).

Of the 307 eligible residents, 227 participated; 118 residents in the intervention group and 109 in the control group. Those who did not participate either refused or were unavailable. Total loss of residents in the 12 months follow-up was 63 (28%), which included 55 deaths [intervention 33 (28%), control 22 (20%)].

The Ethics Committee of the Helsinki University Central Hospital approved the study. Written informed consent was obtained from the residents and/or their closest proxy. All study procedures were consistent with good clinical practice and the World Medical Association Declaration of Helsinki.

Outcome measures

Health outcome measures

The primary health outcome indicator for this cost-effectiveness analysis was change in QALYs, as calculated by combining estimates of health-related quality of life (HRQoL) and life years gained. HRQoL was assessed using the 15-dimensional instrument (15D) with one item covering each of the following dimensions: breathing, mental function, speech, vision, mobility, usual activity, vitality, hearing, eating, elimination, sleeping, distress, discomfort and symptoms, depression and sexual activity. Each dimension was divided into five levels from no problems to extreme problems. These dimensions build a weighted 15D index [31]. The assessments were performed by interviewing the residents or the closest proxy at baseline, and at 6 and at 12 months follow-up.

QALYs were derived from the area under a curve (AUC) calculation for the HRQoL values (15D score) from baseline to the last follow-up, and they ranged from 0 to 1, with 1 being equivalent to full health and 0 equivalent to death. The AUC method assumes a linear change between consecutive HRQoL values at 0, 6 and 12 months. There was one participant in the intervention group whose follow-up observations of 15D were missing. When this participant was excluded from the cost-effectiveness analysis, there appeared to be no discernible effect on the results. For those who died between 6 and 12 months follow-up, the life years gained was assumed to be 6 months, and for those who died before the first follow-up, the life years gained was assumed to be 3 months.

Cost measures

Intervention cost included time use of the educating geriatrician, participating nurses, physician and geriatrician. Travel expenses of the educating geriatrician and preparation costs were also calculated (4 h per session).

Seventeen nurses, one physician and one geriatrician participated in the 4 h sessions. We included 1 h of preparation for every session for each participant. Because the education was arranged during working hours, we valued the working hours of the participants according to the national unit costs of social care and healthcare in Finland [32] including social insurance fees, and converted them to 2019 values using the price index of public expenditure [33]. Study materials were offered electronically at zero cost.

The residents' healthcare services included days spent in assisted living facilities, emergency department visits, outpatient visits, and hospital ward and subacute hospital and rehabilitation days. The data on service utilisation were collected for 12 months and valued according to the national unit costs of social care and healthcare in Finland [32]. The unit costs were converted to 2019 values [33]. Data on primary care physicians' service use were not collected and therefore not included in the analysis. The difference in the medication costs was not statistically significantly different between the groups at the 12 months follow-up and therefore was not included in this analysis. The unit costs of healthcare services and intervention costs are presented in Table 1.

Costs were calculated during the follow-up, and baseline costs for both groups were assumed to be zero, and therefore mean costs were divided by person-years. All costs are expressed in Euros (€) in 2019 prices. As the duration of the study was 12 months, we discounted neither costs nor outcomes.

Statistical methods

Cost-effectiveness

We estimated the incremental cost-effectiveness ratio (ICER), i.e. the ratio of the mean difference in costs to the mean difference in QALYs. The interpretation of ICER is: if the intervention is more costly and more effective, cost-effectiveness is dependent on the decision-makers'

Table 1. Intervention cost and unit costs of healthcare services (in 2019 Euros)

	Unit	Unit cost (€)	Total cost (€)
Intervention cost			
Time use valuation of[a]			
Nurses ($n = 17$)	86 h	25	2,151
Physician ($n = 1$)	5 h	51	255
Participating geriatrician ($n = 1$)	5 h	68	340
Educating geriatrician ($n = 1$)	18 h	68	1,223
Travel cost[b]	4 tickets	3	12
Total intervention cost			3,981
Healthcare services costs[c]			
Assisted living facilities, daily fee		134	
Specialised care			
Emergency department visit		361	
Outpatient visit		301	
Hospital ward, daily fee		896	
Subacute hospital, daily fee		255	

[a]Official Statistics of Finland (OSF) [31]. [b]HSL Helsinki Region Transport ticket (HSL). [c]The national unit costs of social and healthcare in Finland [32].

willingness to pay (WTP) for the extra unit of effectiveness. Conversely, if the intervention is less costly and less effective, cost-effectiveness is dependent on the decision-makers' willingness to accept (WTA) compensation for the lower effectiveness [34].

Statistical comparisons of baseline characteristics between the groups were made using a χ^2 test, *t*-test or bias-corrected bootstrap type *t*-test. Statistical analyses were performed using Stata statistical software version 15 (StataCorp, College Station, TX, USA).

We recognised the skewed distribution of costs at 12 months, the cluster randomisation and the covariate correlation with costs and effectiveness as recommended [35, 36]. We tested the correlation of the cluster's size and participants' baseline characteristics with QALYs and costs. Of the participants' baseline characteristics, 15D score and age were significantly correlated with QALYs and costs. There was no correlation (intraclass correlation coefficient −0.15 for QALYs and −0.16 for costs) within a cluster, and individuals were independent. Therefore, in the cost-effectiveness analysis, we applied bootstrap analysis adjusted with 15D score and age at baseline. In addition, we generated a bootstrapped cost-effectiveness plane for incremental costs and effects (5,000 subsamples).

We conducted one-way sensitivity analyses by changing costs and effectiveness in the intervention group by 15% in either direction. In addition, we conducted sensitivity analysis including only participants alive at the end of the follow-up.

Results

The mean age of the participants was 83 years, and 93% were diagnosed with dementia (Table 2). The participants' cognitive impairment was mainly severe in both groups. At baseline, the residents in the intervention group had a higher number of comorbidities [Charlson comorbidity index (CCI) 3.2 versus 2.5, $P = 0.004$] and lower HRQoL measured by the 15D (0.61 versus 0.66, $P = 0.002$) than those in the control group. The percentage of females in the intervention group was lower than in the control group. The proportion of participants using PIMs was higher in the intervention group (83.1% versus 71.6%, $P = 0.038$).

Costs of intervention and healthcare service use costs

The total intervention costs were €3,981(Table 3). Unadjusted mean total cost of healthcare services per person-year was lower in the intervention group than in the control group during the follow-up, but the difference was not statistically significant (intervention €40,332 versus control €43,251, $P = 0.17$). Costs consisted primarily of the costs of assisted living facilities. There was no statistically significant difference between the groups in any of the healthcare services costs.

Cost-effectiveness

The estimated mean cost per person-year at 12 months follow-up (adjusted with baseline 15D score and age) was €40,954 (95% CI €38,223–€43,686) for the intervention group and €42,584 (95% CI €39,865–€45,302) for the control group (Supplementary Table 1 available in *Age and Ageing* online). The intervention was associated with an average –€1,629 (95% CI −€5,489 to €2,240) higher but not statistically significant costs per person-year compared with the control (Table 4).

Mean QALYs per participant at 12 months follow-up (adjusted with baseline 15D score and age) was estimated to be 0.48 (95% CI 0.45–0.51) in the intervention group and 0.50 (95% CI 0.47–0.53) in the control group (Supplementary Table 1 available in *Age and Ageing* online). The intervention was associated with an average −0.02 (95% CI −0.06 to 0.02) lower but not statistically significant QALYs per participant compared with the control (Table 4).

Table 2. Baseline characteristics

	Intervention group (n = 118)	Control group (n = 109)	P-value
Females, n (%)	77 (65.3)	84 (77.1)	0.050
Mean age, years (SD)	82.9 (7.5)	83.5 (6.9)	0.41
CCI, mean (SD)	3.2 (2.0)	2.5 (1.8)	0.004
MMSE, mean (SD)	8.8 (8.2)	10.0 (8.2)	0.25
15D score, mean (SD)	0.61 (0.12)	0.66 (0.11)	0.002
Number of drugs used regularly, mean (SD)	7.5 (2.8)	7.8 (3.1)	0.79
Proportion using PIM, %	83.1	71.6	0.038
Mean number of PIM (SD)	2.9 (1.8)	2.5 (1.7)	0.28
Mean number of psychotropics (SD)	1.13 (.99)	1.34 (.99)	0.11

Abbreviations: SD, standard deviation; CCI, Charlson comorbidity index; MMSE, Mini-Mental State Examination; 15D, 15-dimensional instrument of health-related quality of life; PIM, potentially inappropriate medication.

Table 3. Unadjusted mean costs (SD) of healthcare services per person-year during the 12 months of follow-up (in 2019 Euros)

	Intervention group (n = 117) Mean €/pyr (SE)	Control group (n = 109) Mean €/pyr (SE)	P-value
Assisted living facilities	39,706 (1,537)	42,541 (1,367)	0.18
Specialized care			
Emergency department visit	83 (22)	72 (20)	0.72
Outpatient visit	82 (23)	86 (18)	0.89
Hospital ward	183 (99)	238 (130)	0.74
Subacute hospital	249 (100)	314 (100)	0.65
Intervention cost	30	0	
Total costs including intervention	40,332 (1,566)	43,251 (1,376)	0.17

Abbreviations: SE, standard error; pyr, person-year.

Table 4. Incremental cost and effectiveness[a] of the educational intervention compared with the control group during the 12 months of follow-up (in 2019 Euros)

	Incremental cost (€/pyr)	Incremental effect (QALYs)	ICER (CI) €/QALY
Base case	–1,629 (−5,489 to 2,240)	−0.02 (−0.06 to 0.02)	83,424 (−233,191 to 803,989)
Sensitivity analysis			
Participants alive at 12 months (intervention n = 84, control n = 87)	67 (−551 to 657)	0.00 (−0.03 to 0.02)	–
Cost (€) +15%	4,579 (464 to 8,702)	−0.02 (−0.06 to 0.02)	Control dominant
Cost (€) –15%	−7,838 (−11,487 to 4,287)	−0.02 (−0.06 to 0.02)	401,299
QALYs +15%	−1,629 (−5,489 to 2,240)	0.05 (0.00 to 0.02)	Intervention dominant
QALYs −15%	−1,629 (−5,489 to 2,240)	−0.09 (−0.13 to 0.05)	17,641

[a]Adjusted with baseline 15D score and age. Abbreviations: pyr, person-year; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; CI, confidence interval

ICER estimation in the base case was €83,424/QALY, and the cost saving was €83,424 per QALY lost in the intervention group compared with TAU (Table 4). The educational intervention was estimated to be less costly and less effective than TAU at 12 months follow-up, and therefore the cost-effectiveness of the educational intervention seemed to be dependent on the decision-makers' WTA.

The bootstrapped cost-effectiveness plane (Figure 1) is positioned mostly in the south–west quadrant, demonstrating a positive ICER value, which shows that the intervention is estimated to be less costly and less effective than TAU. The sensitivity analysis including only participants alive at the end of the 12 months follow-up (Table 4) demonstrates that there was no difference between the groups. The sensitivity analyses also demonstrate that if costs in the intervention

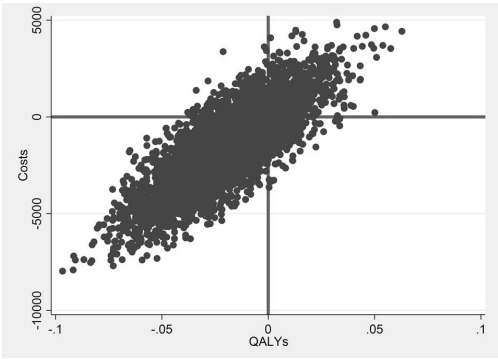

Figure 1. Cost-effectiveness plane

group increase by 15% the control group would dominate. On the other hand, if the effectiveness in the intervention group increases by 15% the intervention group would dominate.

Discussion

This economic evaluation examined the cost-effectiveness of an educational intervention to reduce residents' PIM use in assisted living facilities. Our results indicate that, compared with TAU, this educational intervention was estimated to be less costly and less effective in terms of QALYs. One interpretation here is that cost-effectiveness is dependent on the decision-makers' WTA. However, the differences between costs and QALYs were not statistically significant.

Previously, the educational intervention of this study was shown to reduce PIM use and enhance HRQoL [25]. Outcome measures most adopted in earlier studies were PIM use and QoL; impact on QALYs received less attention [19–24]. We found that PIM use reduction did not seem to translate into improvements in QALYs. This finding is consistent with that of a previous study by Gillespie *et al*. [22], who observed that improvements in PIM use translated into neither QALY gains nor reductions in costs.

QALYs are recognized to have some limitations, although it is claimed to be a common metric that can be applied to any healthcare activity where decision-makers try to maximise health outcomes [37, 38]. It has been argued that it is unsuitable for allocating resources particularly in end-of-life care. Preference-based measures of health valued using death as an anchor point might be inconsequential in a patient group in which death is expected imminently, and potentially desired [39].

Measuring general HRQoL in patients with severe cognitive impairment is complicated, and it has been suggested that both patient- and proxy-reported outcomes should be included to measure the effects of an intervention [40]. In this study, most HRQoL responses were provided by the closest proxy. Thorough validation studies of 15D have shown that the reliability between the proxy and the participant is good and the instrument can be completed by the closest proxy [31, 40]. In addition, other dimensions of QoL, such as social relations and spirituality, may become more important to individuals at the end of life than health status, and HRQoL metrics are unable to measure these dimensions [41]. Mortality among our participants was very high. At 12 months, 33% of the residents in the intervention group had died compared with 22% of participants in the control group [25]. This might explain our finding that HRQoL declined more slowly in the intervention group but QALYs per patient were lower in the intervention group compared with TAU.

Our results differ from the findings of earlier economic evaluations of educational interventions that observed the interventions as being more effective and less costly [19, 20]. However, the study populations and outcome measures differ. For example, Ballard *et al*. [20] included older people with dementia living in nursing homes, but only those alive at the end of the follow-up. Sanyal *et al*. [19] included only community-dwelling people. On the other hand, the intergroup differences diminished in our sensitivity analysis with the population alive at the end of the follow-up. This drop indicates that differences in costs and QALYs were mostly dependent on mortality, and not on the intervention itself.

Our results are subject to some other sources of uncertainties. First, costs and QALYs, as well as ICER, had wide CIs and the differences between the groups are not statistically significant. In addition, the widely spread cost-effectiveness plane established the possibility that there is no difference between the arms.

Second, old age and morbidity were associated with a high mortality rate. At baseline, compared with the control, the intervention group had lower HRQoL, higher morbidity and a higher proportion using PIMs. Overall, the intervention group was frailer at baseline. From all the baseline characteristics, only HRQoL and age were correlated with the outcome measures. We tested the effects of all the characteristics on the results, and methods appropriate for cRCT economic evaluations helped reduce bias caused by the study design [35, 36]. It is still possible that there are some non-observable individual covariates, for example social relations. Third, because costs were calculated only during the follow-up, baseline costs for both groups were assumed to be zero. Therefore, costs were divided by the person-years. In addition, costs for residents' healthcare service use were lacking complete details, and societal costs were not included.

WTA is typically used to indicate the minimum monetary amount required to forgo the health benefit from implementing the intervention. For the educational intervention to be cost-effective, it could well be that a decision-maker would require that the intervention would be more effective or achieve bigger savings compared with the control group. Earlier contingent valuation studies have found that WTA might also exceed WTP in healthcare; they have also proffered explanations for the disparity [34, 42, 43]. Therefore, the results of this study need to be treated with caution.

Previous research has been restricted to short-term effectiveness of interventions, but evidence is lacking regarding the sustainability of implementation. This educational intervention has demonstrated a positive impact on PIM use, which however appears to diminish at 12 months [25]. This might partly stem from nursing staff turnover, as training was not provided on a continuous basis. In addition, not all nurses in the intervention group participated in these sessions. A higher level of participation would have increased the intervention costs, but it might have gained better effectiveness in the intervention group.

The educational intervention could be considered as quite minimal and also feasible, and intervention costs were only around €30 per participant. To achieve sustainable effectiveness in implementation, educational intervention could be organised on a more continuous basis targeted for nurses and physicians. In practice, nurses play a key role in identifying medical-related problems in assisted living facilities whereas physicians make the final decision about medications based on assessing the risks and benefits.

This economic evaluation indicates that the educational intervention was estimated to be less costly and less effective in terms of QALYs compared with TAU. The reduction in PIMs did not seem to translate into improvements in QALYs although HRQoL declined more slowly in the intervention arm. Our study illustrates the apparent difference in HRQoL and QALY in a very frail long-term care population close to death. This emphasises that further research into the impact of reducing PIM use on health outcomes is needed.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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ARTICLE III

Rantsi Mervi, Kortelainen Lauri, Hyttinen Virva, Jyrkkä Johanna & Kankaanpää Eila. Trends in the use of psychotropics in older people with dementia: Interrupted time series of Finnish clinical guidelines of behavioural and psychological symptoms of dementia. Age Ageing. 2023 Jun 1;52(6):afad094. DOI: 10.1093/ageing/afad094.

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RESEARCH PAPER

Trends in the use of psychotropics in older people with dementia: interrupted time series of Finnish clinical guidelines of behavioural and psychological symptoms of dementia

Mervi Rantsi[1], Lauri Kortelainen[1], Virva Hyttinen[1], Johanna Jyrkkä[2], Eila Kankaanpää[1]

[1]Department of Health and Social Management, University of Eastern Finland, Kuopio, Finland
[2]Information and Development Services Unit, Finnish Medicines Agency, Helsinki, Finland

Address correspondence to: Mervi Rantsi. Tel: +358 46 920 2963. Email: mervi.rantsi@uef.fi

Abstract

Background: Up to 90% of people with dementia experience behavioural and psychological symptoms of dementia (BPSD) as part of their illness. Psychotropics are not recommended as the first-line treatment of BPSD because older people are more prone to adverse reactions. In this study, we evaluate the impact of the Finnish clinical guidelines of BPSD (published in 2017) on psychotropic use in people with dementia.
Methods: This study is based on Finnish Prescription Register data from 2009 to 2020. The data included all community-dwelling Finnish people aged ≥65 and who had anti-dementia medication purchases ($n = 217{,}778$). We used three-phased interrupted time series design to evaluate the changes in levels and trends of monthly ($n = 144$) psychotropic user rates compared with the predicted trends. In addition, we evaluated the changes in levels and trends of monthly new psychotropic user rates.
Results: The level of monthly psychotropic user rate decreased non-significantly during the intervention period (β −0.057, $P = 0.853$), and during the post-intervention period, there was an increase in the level (β 0.443, $P = 0.091$) and slope (β 0.199, $P = 0.198$), but not statistically significant. The level of monthly new psychotropic user rate (β −0.009, $P = 0.949$) during the intervention period and the level (β 0.044, $P = 0.714$) and slope (β 0.021, $P = 0.705$) during the post-intervention period were almost unchanged.
Conclusions: Results may indicate possible challenges in deprescribing and better adherence to the guidelines at the beginning of BPSD treatment. Further research into the barriers to implement BPSD guidelines and the availability of non-pharmacological treatments is needed.

Keywords: psychotropics, behavioural and psychological symptoms of dementia, clinical guidelines, interrupted time series, impact, older people

Key Points

- Psychotropics are not recommended in the treatment of behavioural and psychological symptoms of dementia (BPSD).
- We evaluated the impact of the Finnish clinical guidelines of BPSD using registry-based data of the dementia population.
- We used three-phased interrupted time series design to evaluate the levels and trends of monthly psychotropic user rates.
- Finnish clinical guidelines of BPSD did not decrease the trend or level of psychotropic users in 2009–20.
- Research into the barriers to implement BPSD guidelines and the availability of non-pharmacological treatments is needed.

Introduction

Around 55 million people worldwide suffer from dementia, and the prevalence is expected to increase [1]. Up to 90% of people with dementia develop behavioural and psychological symptoms of dementia (BPSD) during their illness [2, 3]. BPSD is a broad term for symptoms including mood disorders, depression, agitation, psychosis, sleep disturbances, anxiety, apathy, dysphoria, aberrant motor activity, hallucinations and delusions [2, 4, 5]. BPSD decreases the well-being of people with dementia and causes admissions to institutional care [6]. Clinical guidelines of BPSD recommend non-pharmacological interventions, such as caregiver training, modification of environmental factors, individualised therapy, exercise, music therapy or massage; initiation of psychotropics is recommended only in case of failure of non-pharmacological interventions [7, 8].

Older people with dementia are more prone to adverse reactions, and the use of psychotropics has been associated with potential harms including falls, fractures and mortality [9, 10]. Especially antipsychotics have been associated with increased mortality [9, 11], amongst other adverse events [12, 13]. However, rates of psychotropic use in older people with dementia are high. A recent meta-analysis estimated that 33% of nursing home residents received two or more psychotropics [14]. In the UK, 47% of older people with dementia were prescribed one or more psychotropics and 18% were prescribed antipsychotics in 2007 [15], but the prevalence of antipsychotics decreased in the 2010s [16]. In Denmark, 25% of patients with dementia were estimated to receive treatment at least two psychotropics [17]. Of Finnish people diagnosed with Alzheimer's disease, 53% purchased at least one psychotropic, 20% purchased antipsychotics [18] and 18% used concomitantly two or more psychotropics over a 6-year period [19].

Recent literature has recognised the need for evaluation of clinical guidelines aiming to reduce the use of potentially inappropriate medication in older people [20, 21]. Registry-based studies of the impacts of clinical dementia guidelines are rare and there is only little evidence of changes in trends of psychotropic use amongst older people with dementia in nursing home environments [22–25]. The Ontario Drug Benefit programme slowed the growth of atypical antipsychotics use amongst patients with dementia, but it did not reduce the prescription rate [25]. Safety warnings about antipsychotics in France were followed by a reduction in antipsychotic use in people with dementia [24]. Studies from the USA found decreased antipsychotics use following the National Partnership to Improve Dementia Care in nursing homes [22] and in long-term care [23]. However, Maust *et al.* [23] reported the decrease already before the start of the partnership, and Gerlach *et al.* [22] found that at the same time the use of other psychotropics and opioids increased.

This study aimed to evaluate the impact of the Finnish clinical guidelines of BPSD (later the BPSD guidelines) on psychotropic use in older community-dwelling people with dementia. The Finnish Current Care Guidelines of Memory disorders were originally published in 2006, but without recommendations for the treatment of BPSD [26]. In September 2016, the Finnish Medical Society Duodecim published an evidence summary article about non-pharmacological treatments in the care of BPSD [27], and in January 2017, they published the BPSD guidelines. In addition, Duodecim supported the dissemination of the guidelines by providing educational material and organising short education events at two Finnish Medical Conventions in 2017. According to the BPSD guidelines, the primary management of BPSD is with non-pharmacological interventions. Psychotropics, especially antiepileptics and antipsychotics, should be avoided or used only in short-term, and their need should be evaluated every 3–6 months [26].

Methods

Data source

We used Finnish Prescription Register from the years 2009 to 2020. The register maintained by the Social Insurance Institution of Finland (SII) includes all prescription medication purchases of community-dwelling people receiving reimbursements. The data were linked to the Care Registers for Social and Health Care (National Institute for Health and Welfare) and causes of deaths (Statistics Finland). Data source is described in detail in Supplementary Text 1.

Study population

The study population included people aged ≥65 years with dementia during the follow-up period. We defined people with dementia as ATC-class N06D anti-dementia medication (Supplementary Table 1) users (n = 217,778). People with dementia diagnoses not on anti-dementia medication are not included in this study because the Finnish Prescription Register does not contain information of the diagnoses. In 2012, around 4% of people with dementia diagnoses had no anti-dementia medication [30], and the onset of anti-dementia medication has increased in the past decade [31].

We divided the 12-year study period into 144 observation months, from January 2009 to December 2020. For each month (1st day), we created a cohort of people with anti-dementia medication, alive and not in long-term inpatient care.

Outcome measures

The main outcome variable was the monthly psychotropic user rate of the overall dementia population. Psychotropics were classified [26, 29] as antipsychotics (ATC-N05A), antidepressants (ATC-N06A), anxiolytics (ATC-N05B), hypnotics (ATC-N05C) and antiepileptics (N03AF02, N03AG01 and N03AX16). We analysed these psychotropics separately and in total.

To analyse the monthly psychotropic user rates, we defined use periods. Each individual's first psychotropic purchase (of interest) was the beginning of a use period.

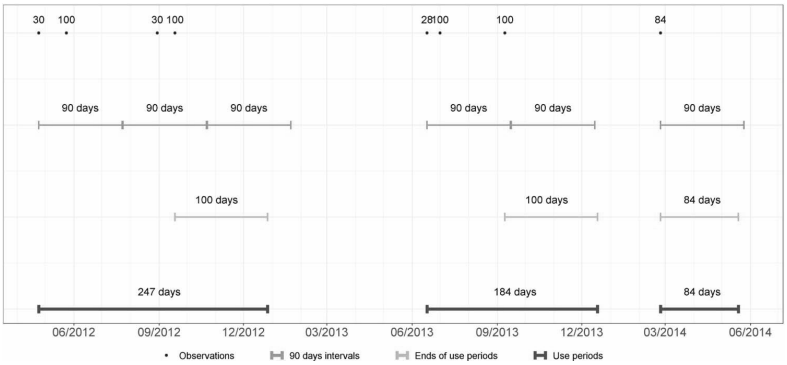

Figure 1. Example of a random individual's psychotropics use period determination.

The individual was followed for 90 days, and if she/he had at least one psychotropic purchase during the period, it was extended by a further 90 days, otherwise it ended. The end of the use period was defined based on the medicines' package size multiplied by the number of packages, and it was limited to be between 7 and 100 days. Data did not include the daily doses of individuals' purchase patterns and we assumed that they used one unit per day [32]. An example of a random individual's use period determination is presented in Figure 1. The maximum length of the use period was based on the reimbursement regulation in Finland. Individuals can buy medicine for no more than 3 months of treatment at one time [33].

The secondary analysis concerned individuals who had no psychotropic (of interest) purchases during the 12 months prior to the measurement month (the monthly new user rate of the overall dementia population). In Finland, prescriptions of medicines affecting the central nervous system (i.e., psychotropics) are valid for 1 year [34]. Therefore, individuals may purchase prescription medications without a physician's up-to-date assessment, and here we reduced this possible bias by considering only the new psychotropic users.

Statistical analysis

We used three-phased interrupted time series (ITS) design to evaluate the changes in levels and trends of psychotropic users. Monthly rates of psychotropic users were evaluated from January 2009 to December 2020. The study period was divided into three phases: pre-intervention period (time before publication of the article about BPSD [27], 1/2009–9/2016, $n = 93$), intervention period (time from the article about BPSD [27] to the BPSD guidelines publication [26], 10/2016–1/2017, $n = 4$) and post-intervention period (time after the BPSD guidelines, 2/2017–12/2020, $n = 47$). We observed seasonality, autocorrelation and non-stationary white noise in the data (Supplementary Figure 1), and we used the seasonal autoregressive integrated moving average (ARIMA) model to consider these issues [35]. Model estimation is explained in detail in Supplementary Text 2.

The time needed for clinical guidelines to reach the physicians is unknown, and it is expected to take time after the publication. Therefore, we tested the robustness of our main findings by setting the intervention timepoint to January 2018. In addition, we conducted a robustness check in which we excluded the year 2020 because COVID-19 might have increased medication use [28].

All analyses were made with R V4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) using a package fable [37]. We considered a P-value of <0.05 to be statistically significant.

Results

Descriptive statistics

The study sample included 217,778 people with antidementia medication in total, and the number increased from 43,750 in 2009 to 105,683 in 2020 (Table 1). Mean age of the population was 82.7 years (range 81.7–83.4 years) and 65.3% were female (range 63.3–67.1%). On average, 53.5% of the population used at least one psychotropic during 2009–20 (range 50.6–57.2%).

Impact of clinical guidelines of BPSD on the monthly psychotropic user rates

The mean monthly psychotropic user rate was 43.8% (SD 1.76) during the pre-intervention period and 41.7% (SD 0.3) during the post-intervention period (Table 2). Although the level of monthly psychotropic user rate decreased non-significantly during the intervention period (β −0.057, $P = 0.853$), it did not continue to the post-intervention period. We found a non-significant increase in the level (β 0.443, $P = 0.091$) and slope (β 0.199, $P = 0.198$) of all psychotropic users during the post-intervention period. There was no change in the observed trend during the post-intervention period compared with the predicted trend (Figure 2A).

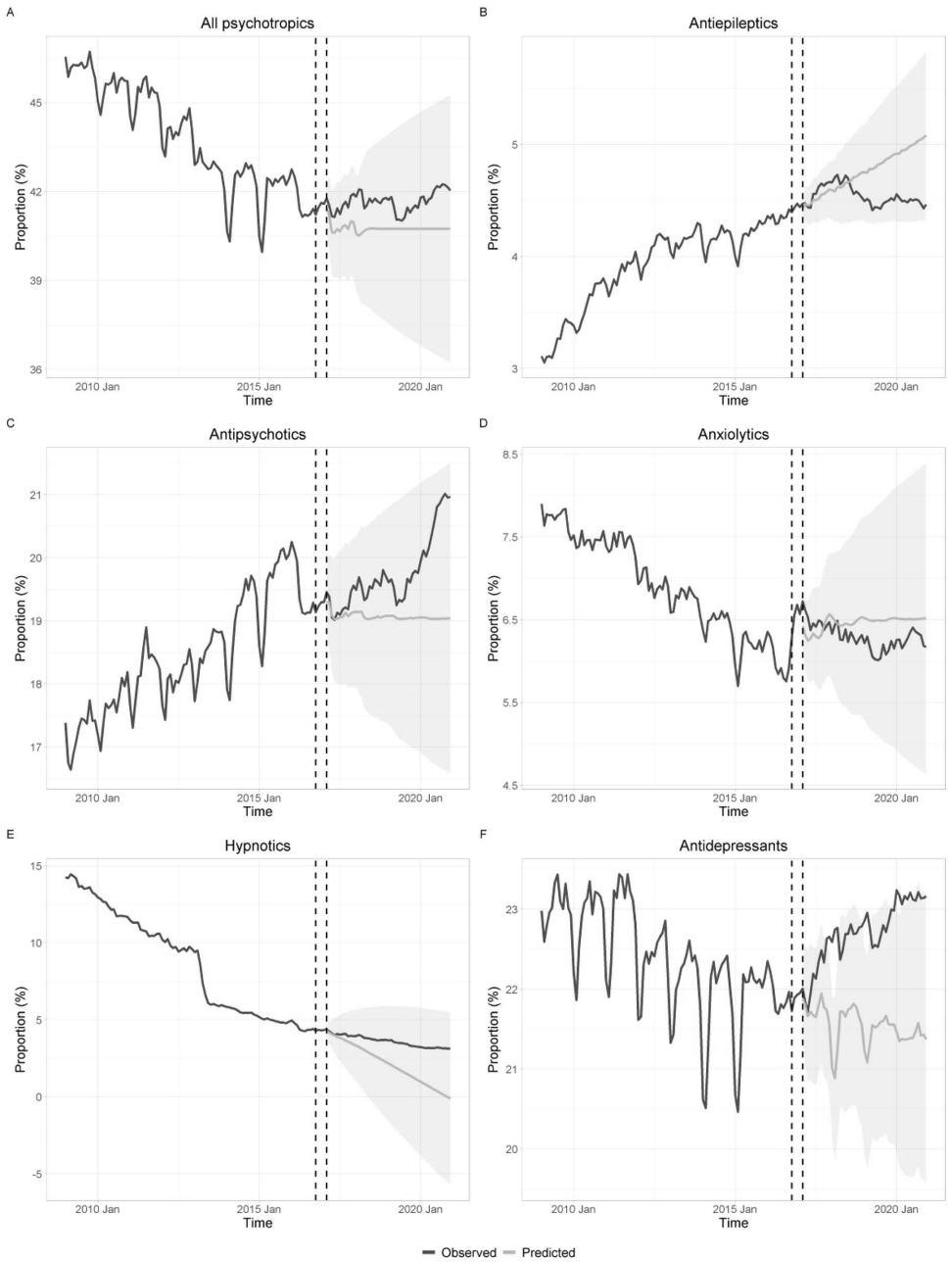

Figure 2. Panels A-F observed and predicted trends of all psychotropics users with 95% prediction intervals.

Table 1. Characteristics of the study population (years 2009–20)

	Older people with dementia[a]			Older people with dementia using any psychotropics[b]		
	Total (*n*)	Female (*n*, %)	Age, years (mean, SD)	Total (*n*, %)	Female (*n*, %)	Age, years (mean, SD)
2009	43,750	29,354 (67.1)	81.7 (6.1)	25,024 (57.2)	17,576 (70.2)	81.8 (6.1)
2010	48,440	32,463 (67.0)	82.0 (6.2)	27,616 (57.0)	19,404 (70.3)	82.1 (6.2)
2011	53,446	35,677 (66.8)	82.3 (6.3)	30,160 (56.4)	21,028 (69.7)	82.4 (6.3)
2012	64,871	43,013 (66.3)	82.4 (6.4)	35,745 (55.1)	24,832 (69.5)	82.5 (6.4)
2013	72,818	48,000 (65.9)	82.6 (6.5)	39,065 (53.6)	27,050 (69.2)	82.7 (6.5)
2014	81,025	52,993 (65.4)	82.8 (6.6)	43,140 (53.2)	29,587 (68.6)	82.9 (6.6)
2015	87,384	56,761 (65.0)	83.0 (6.7)	45,718 (52.3)	31,243 (68.3)	83.1 (6.7)
2016	93,162	60,237 (64.7)	83.1 (6.8)	48,049 (51.6)	32,661 (68.0)	83.3 (6.8)
2017	97,688	63,004 (64.5)	83.2 (6.9)	49,847 (51.0)	33,662 (67.5)	83.3 (6.9)
2018	101,650	65,203 (64.1)	83.3 (6.9)	51,907 (51.1)	34,833 (67.1)	83.4 (6.9)
2019	104,020	66,270 (63.7)	83.3 (7.0)	52,658 (50.6)	35,177 (66.8)	83.5 (7.0)
2020	105,683	66,932 (63.3)	83.4 (7.0)	54,488 (51.6)	36,126 (66.3)	83.5 (7.0)

[a]Anti-dementia medicines (ATC-N06D) users. [b]Antipsychotics (ATC-N05A), antidepressants (ATC-N06A), anxiolytics (ATC-N05B), hypnotics (ATC-N05C) and antiepileptics (N03AF02, N03AG01 and N03AX16). SD, standard deviation

The monthly user rates were highest for antipsychotics and antidepressants (Table 2). The levels of user rates decreased non-significantly during the intervention period, and there were upward trends during the post-intervention period (Figure 2C, F). Hypnotic user rates had a marginally downward trend in all periods, but not compared with the predicted trend during the post-intervention period (Figure 2E). In contrast, the level of anxiolytic user rate increased during the intervention period (β 0.304, $P = 0.02$) and there was a downward trend during post-intervention period, but not compared with the predicted trend (Table 2 and Figure 2D). The monthly antiepileptic user rate was the lowest and there was a non-significant decrease in the rate during the intervention period (β −0.061, $P = 0.216$). In contrast to other psychotropic groups, the observed trend of antiepileptic users was downward compared with the predicted trend during the post-intervention period (Figure 2B).

Secondary analysis

The mean monthly new psychotropic user rate was 1.7% (SD 0.26) during the pre-intervention period and 1.4% (SD 0.13) during the post-intervention period (Table 2). The level of new psychotropic user rate (β −0.009, $P = 0.949$) during the intervention period and the level (β 0.044, $P = 0.714$) and trend during the post-intervention period were almost unchanged (Table 2 and Figure 3A). However, the observed trends were below the mean predicted trends during the post-intervention period, but they fell inside prediction intervals (Table 2 and Figure 3A–F).

In the robustness check in which the intervention timepoint was January 2018, as opposed to the increased level in the main analysis (step 2 in Table 2), we found no change in the level of psychotropic users (β −0.021, $P = 0.938$) (Supplementary Table 2). However, the post-intervention increased slope (β 0.065, $P = 0.047$) was similar to that observed in the main findings. For antiepileptic users, the decreased slope (β −0.025, $P = 0.005$) was similar to the main findings and statistically significant. For other psychotropics, the changes in levels and trends were very small and non-significant in both analyses. In the robustness check in which the year 2020 was excluded, the levels and trends of psychotropic users were similar to those in the main findings (Supplementary Table 3).

Discussion

We evaluated the impact of the Finnish clinical guidelines of BPSD [26] using registry-based data of the dementia population. Our results showed that the monthly psychotropic user rate decreased non-significantly at the intervention period, but there was an upward trend during the post-intervention period, which indicate that the clinical guidelines of BPSD publication had no impact on the psychotropic use. On the other hand, monthly new psychotropic user rates were almost unchanged during the intervention period, and the trend was below the predicted trend during the post-intervention period. Overall, the changes in the levels and trends were very small and non-significant.

Antiepileptic users were the only psychotropic group in which the observed trend was downward compared with the predicted trend during the post-intervention period, which is encouraging because antiepileptics are the last-line treatment for BPSD [26]. On the other hand, the monthly antipsychotic user rate increased in 2020, in the beginning of the COVID-19 pandemic. Campitelli *et al*. [38] reported similar findings, and they concluded that this could be explained by social isolation and loneliness as well as fewer available non-pharmacological options. However, our findings from the robustness check, in which we excluded the year 2020, were similar to our main findings.

Earlier studies of the impact of dementia guidelines were conducted in nursing home environments, and our study is the first to consider the community-dwelling population.

Table 2. Monthly rates and changes in levels and trends of all psychotropic users and new users

	Pre-intervention period	Intervention period	Step 1		Ramp 1		Post-intervention period	Step 2		Ramp 2	
	Mean (SD) observed monthly rate of users, %	Mean (SD) observed monthly rate of users, %	Parameter estimate, β (95% CI)	*P* value	Parameter estimate, β (95% CI)	*P* value	Mean (SD) observed monthly rate of users, %	Parameter estimate, β (95% CI)	*P* value	Parameter estimate, β (95% CI)	*P* value
	(n = 93)	(n = 4)					(n = 47)				
All users											
All psychotropics	43.76 (1.76)	41.47 (0.18)	−0.057 (−0.665, 0.550)	0.853	−0.167 (−0.461, 0.13)	0.266	41.66 (0.33)	0.443 (−0.068, 0.953)	0.091	0.199 (−0.103, 0.50)	0.198
Antidepressants	22.37 (0.67)	21.87 (0.10)	−0.304 (−0.748,0.139)	0.181	0.078 (−0.166, 0.322)	0.532	22.71 (0.38)	0.178 (−0.182, 0.539)	0.334	−0.039 (−0.273, 0.195)	0.743
Antipsychotics	18.44 (0.91)	19.24 (0.08)	−0.227 (−0.651, 0.197)	0.296	−0.034 (−0.258, 0.190)	0.767	19.74 (0.56)	0.079 (−0.277, 0.436)	0.664	0.077 (−0.150, 0.304)	0.507
Hypnotics	8.71 (3.37)	4.33 (0.03)	−0.164 (−0.471, 0.144)	0.298	0.091 (−0.159, 0.341)	0.476	3.62 (0.36)	0.151 (−0.129, 0.431)	0.293	−0.020 (−0.273, 0.233)	0.876
Anxiolytics	6.89 (0.60)	6.52 (0.17)	0.304 (0.043, 0.565)	0.024	0.102 (−0.005, 0.208)	0.063	6.30 (0.15)	0.134 (−0.089, 0.357)	0.241	−0.090 (−0.197, 0.018)	0.104
Antiepileptics	3.93 (0.37)	4.44 (0.03)	−0.061 (−0.158, 0.035)	0.216	0.010 (−0.041, 0.061)	0.698	4.54 (0.09)	0.086 (−0.004, 0.176)	0.062	−0.022 (−0.073, 0.030)	0.412
New users											
All psychotropics	1.721 (0.258)	1.538 (0.062)	−0.009 (−0.284, 0.266)	0.949	−0.022 (−0.128, 0.084)	0.681	1.366 (0.127)	0.044 (−0.191, 0.279)	0.714	0.021 (−0.087, 0.129)	0.705
Antidepressants	0.959 (0.127)	0.874 (0.032)	−0.035 (−0.216, 0.146)	0.703	−0.004 (−0.068, 0.060)	0.908	0.824 (0.085)	−0.038 (−0.183, 0.108)	0.612	0.003 (−0.063, 0.068)	0.934
Antipsychotics	1.023 (0.107)	0.930 (0.040)	−0.039 (−0.196, 0.118)	0.626	−0.001 (−0.056, 0.054)	0.970	0.881 (0.081)	−0.039 (−0.165, 0.087)	0.544	0.002 (−0.054, 0.057)	0.952
Hypnotics	0.552 (0.221)	0.297 (0.032)	−0.001 (−0.123, 0.121)	0.990	0.002 (−0.052, 0.057)	0.930	0.222 (0.028)	−0.024 (−0.132, 0.084)	0.666	−0.003 (−0.059, 0.053)	0.924
Anxiolytics	0.569 (0.075)	0.777 (0.069)	0.191 (0.045, 0.338)	0.012	0.046 (−0.005, 0.098)	0.080	0.645 (0.057)	−0.298 (−0.408, −0.189)	0.000	−0.044 (−0.096, 0.007)	0.094
Antiepileptics	0.234 (0.030)	0.234 (0.021)	−0.025 (−0.083, 0.034)	0.407	0.009 (−0.012, 0.029)	0.405	0.207 (0.029)	−0.006 (−0.052, 0.041)	0.815	−0.010 (−0.030, 0.010)	0.342

Step 1 = change in level immediately following publication of the guidelines in September 2016. Ramp 1 = gradual slope change relative to the slope in the period prior to publication of the guidelines in September 2016. Step 2 = change in level immediately following publication of the guidelines in January 2017. Ramp 2 = gradual slope change relative to the slope in the period prior to publication of the guidelines in January 2017.

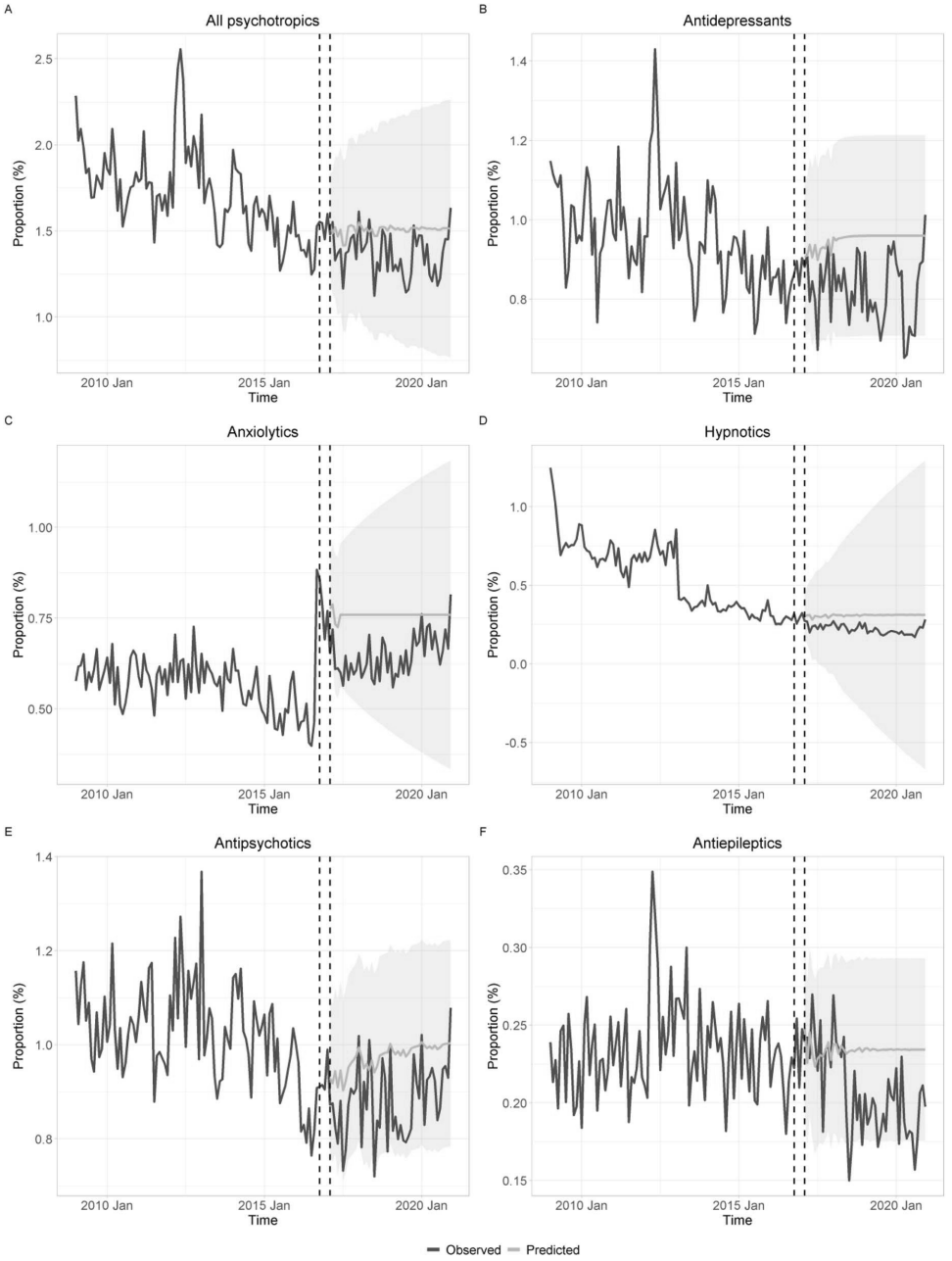

Figure 3. Panels A-F observed and predicted trends of new psychotropics users with 95% prediction intervals.

Our findings are rather consistent with previous results from Canada, where no reduction was found in the rate of psychotropics after safety warnings [25]. On the other hand, studies from the USA and France [22–24] found a decline in the use of antipsychotics after guidelines. However, Maust *et al*. [23] concluded that the National Partnership to Improve Dementia Care itself did not appear to accelerate the decline, and Gerlach *et al*. [22] reported

that at the same time the use of other psychotropics and opioids increased. Similarly, we found increasing trend of antidepressant use at the same time with decreasing trend of hypnotic use. This could partly be explained by physicians replacing hypnotics with antidepressants [39]. Psychotropics have other acknowledged indications than BPSD [40], and this is a challenge when using the SII Prescription Register with no information concerning the patient's diagnosis.

Population-based cohorts are rare in the evaluation of the long-term impact of clinical guidelines [20, 21], and one strength of our study is that our data cover all community-dwelling Finnish people with anti-dementia medication and older than 65 years. Another strength is that, to the best of our knowledge, our study is the first to evaluate the impact of BPSD guidelines on new psychotropic users. Our results were different for all users and new users; whereas the trends of all users were upward compared with the predicted trends during the post-intervention period, for new psychotropics users the trends were unchanged. This could indicate challenges in deprescribing and better adherence to the guidelines at the beginning of BPSD treatment.

The strength of our analysis is that we used the seasonal ARIMA model to reduce the possible bias caused by non-stationarity [35, 36]. Although ITS is considered to be a reliable design for evaluating the impacts of health policies, it does not provide protection against the impact of other events occurring at the same time [41, 42]. Changes in reimbursements and medication prices may have an impact on medication use and prescribing practice in long term [32, 43]. There are many factors influencing the treatment of BPSD, such as coping with BPSD of carers, care staff and patients with dementia [40]. Physicians may recommend non-pharmacological treatments, but their implementation is the responsibility of the whole staff and there can be a lack of resources or knowledge [44]. Complex causes of BPSD should be carefully considered, and the Finnish current care guideline of memory disorders, like many other dementia guidelines, recommends personalised care plan in dementia care. Nevertheless, strategies engaging stakeholders to person-centred care and approaches tailored to care givers, and behavioural and environmental approaches should be better integrated into dementia care [45, 46].

It is noteworthy that the use of anti-dementia medications increased during the study period. This can be seen as an indication of adherence to the BPSD guidelines as anti-dementia medications are the first-line pharmacological treatments for BPSD [26]. However, this increase can also be explained by increased dementia prevalence, ageing of the population and changes in the service system. During the follow-up, the share of assisted living facilities with 24-h assistance in a home-like environment has increased and the share of long-term inpatient care has decreased [47], but our data did not contain the community-dwelling persons precis form of living and care. Consequently, the Prescription Register had every year a higher proportion of older people whose medication purchases were reimbursed by the SII. This may underestimate the change caused by the BPSD guidelines in the use of psychotropics since the prevalence of psychotropic use is higher in institutionalised care [48, 49].

Our results are subject to some other sources of uncertainties. First, clinical guidelines are challenging interventions to examine because there is no exact timepoint of implementation [41]. Many factors that can take months or even years can influence the performance (such as when the physician sees the guidelines, the patient visits the physician or the medication is assessed). To check the robustness of our findings, we changed the cut-off to 2018, after which the results were partly more significant and there was a small decrease in the level of psychotropics users.

Second, the SII Prescription Register data are exposed to the effect of stockpiling [50, 51]. Our definition of 90-day use periods was based on the reimbursement regulations and the recommendation of the BPSD guidelines to check the medication of dementia patients once in 3–6 months [26]. With this use period, there is a small possibility that for some individuals the use period was underestimated because of stockpiling. A person could have made several purchases during the use period and consequently the use period could have been longer. Third, we defined the dementia population based on anti-dementia medication use. The Prescription Register does not include information of dementia diagnosis, BPSD diagnoses or their severity. We assumed that people with dementia experience BPSD [2, 3]. Fourth, our analyses are based only on the use of psychotropics and we had no information concerning the availability of non-pharmacological treatments.

BPSD causes admission to inpatient care and lowers both the patients' and the care givers' well-being [6]. Clinical guidelines are essential to ensure quality-of-care, but to achieve better quality in dementia care, there is a need for other actions. To improve adherence to the BPSD guidelines, there is a need for further research into barriers to and facilitators for implementation of the BPSD guidelines and a need to ensure the availability of non-pharmacological interventions. Recent systematic review of implementation strategies that aimed at increasing the use of non-pharmacological interventions has provided evidence that positive outcomes for BPSD are achievable when multiple implementation strategies are employed. Strategies commonly consisted of partnerships between organisations, access to new funding, educational strategies and support for interventionists [52]. In practice, physicians make the decision about medications, and they have their place, especially for the management of acute situations where stakeholders' safety may be at risk. Therefore, reduction in psychotropic use should not be used as the only metric of best practice [45]. The whole multi-professional staff plays a key role in providing non-pharmacological interventions, and there is a need for implementation of non-pharmacologic interventions and educating care givers about behavioural and environmental approaches.

Conclusions

This population-based registry study indicates that the Finnish clinical guidelines of BPSD did not decrease the trend or level of psychotropic users in older community-dwelling people with dementia in 2009–20. On the other hand, trends of new psychotropic users were unchanged after publication of the BPSD guidelines. This may indicate possible challenges in deprescribing and better adherence to the guidelines at the beginning of BPSD treatment. Further research into the barriers to implement BPSD guidelines and into the availability of non-pharmacological treatments and implementation strategies to support person-centred BPSD care are needed.

Ethics Statement: According to Finnish legislation, no ethics committee approval was required as data were pseudonymised by the register maintainers before submission to the research team. We obtained appropriate permissions to access the data from each register maintainer (SII, THL and Statistics Finland).

Declaration of Conflicts of Interest: None.

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Data Availability Statement: Due to its proprietary nature, supporting data cannot be made openly available. Further information about the data and conditions for access are available at the Finnish Social and Health Data Permit Authority Findata.

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ARTICLE IV

Rantsi Mervi, Blankart Katharina, Kortelainen Lauri, Jyrkkä Johanna & Hyttinen Virva. Influence of physician peer network and the Finnish Clinical Guidelines on Memory Disorders on prescribing of psychotropic. Manuscript.

MERVI RANTSI

Effective implementation of evidence-based practices and de-implementation of low-value care are crucial for improving health outcomes. Strengthening the role of health economics in implementation research is recommended to enhance resource allocation and value in healthcare. This dissertation uses economic evaluation and quasi-experimental study designs in the evaluation of implementation strategies for reducing potentially inappropriate medications in older people with dementia.

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