A Fine Balance: Drug Use in Norwegian Nursing Homes

Christine Gulla

Thesis for the Degree of Philosophiae Doctor (PhD)
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…there are three core requirements for success in medicine: diligence, to do right, and ingenuity.

Atul Gawande

Better: A surgeon's Notes on Performance

Scientific environment

This research project was performed at Centre for Elderly and Nursing Home Medicine (SEFAS) and Research Group for General Practice at Department of Global Public Health and Primary Care, University of Bergen. The PhD was funded by the Research Council of Norway through the COSMOS study. The COSMOS study was funded by the Research Council of Norway, Rebekka Ege Hegermann's Endowment, and the University of Bergen.

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Co supervisors

Associate Professor Elisabeth Flo, Department of Clinical Psychology, University of Bergen.

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Courses

I have attended PhD courses at the University of Bergen and the University of Oslo, and taken courses organized through the Norwegian Medical Association, Research school for Pharmacy, and Queen Maud University College. I have also participated in the Norwegian Research School in General Practice.

Content

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First, I would like to thank the participating patients, nursing home staff, managers, and physicians. The extra effort you made brings research on nursing home patients one step further. You did a great, important job and gave me the inspiration to carry out this project.

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Introduction

Nursing homes and elderly people have been a part of my life since I was a child. I remember coming to work with my mum and experiencing that adults lived in nursing homes and ate ice cream because they lacked teeth, and that there was something called adult diapers. Since then I have expanded my insight into their world and aquired a fond interest for the elderly.

The nursing home patients are among the frailest people in our community [1]. They have lived long lives and accumulated diseases and conditions over the years. Almost everyone has been in contact with numerous physicians and different levels of care. Many are sent back and forth between the nursing home, out-of-hour services, and the hospital [2]. These factors complicate treatment and can lead to polypharmacy [3].

Polypharmacy is often defined as using five or more drugs. This is rather the norm in the nursing homes, given that the average numbers of drugs are seven to eight [4, 5].

Two of the major groups of prescribed drugs are antihypertensive drugs and psychotropic drugs. Research on the effect of these drugs in nursing home patients is either lacking or shows conflicting results [6-8]. The appropriateness of antihypertensives and psychotropics is therefore often questioned. Multiple interventions aiming to optimize prescriptions have been tested. Six recent reviews all aimed to investigate which interventions were effective [9-14]. Their conclusion is that prescribing could be improved, and there is most support for educational approaches. Most of the interventions are complex interventions consisting of multiple professions and steps. Complex interventions, and many involved professions are factors that are known to affect implementation, and thus the outcome of the intervention [15].

To bring the research forward, we wanted to optimize prescribing by the COSMOS approach (Figure 1). The COSMOS study aimed to improve the quality of life for nursing home patients in an effectiveness-implementation cluster randomized clinical

hybrid trial. Five interventions create the COSMOS acronym; COmmunication, Systematic pain assessment and treatment, Medication review, Organization of activities, and Safety. During the study, these interventions were implemented in 67 nursing home units across Norway. The intervention consisted of education of nursing home staff, systematic assessment and support regarding barriers and promoters, clinical assessment of the patient's symptoms and function, and medication reviews with collegial mentoring. In the medication reviews, we used the elements usually available in medication reviews: explicit prescribing criteria, clinical tests, diagnoses, medical records, and lab tests. In addition, we had available systematic assessment of pain, cognition, neuropsychiatric symptoms (NPS), function, and quality of life. As a part of the study, the staff talked with the patients and relatives about the diseases, prognosis, and goals of care, and organized individualized activities for each patient. These pieces, together with an emphasis on documentation and follow-up, could increase safety.

Figure 1 **The COSMOS logo**

The opportunity to be a part of a trial focusing on many aspects of life for the nursing home patients initially brought me into this PhD programme. After four years, I want to share a piece of the picture with you. With this thesis, I aim to describe the method and implementation of the medication reviews in the COSMOS study and explore how to optimize prescribing for two of the major drug groups contributing to polypharmacy.

List of publications

Paper 1

Gulla C, Selbaek G, Flo E, Kjome R, Kirkevold O, Husebo BS. Multi-psychotropic drug prescription and the association to neuropsychiatric symptoms in three Norwegian nursing home cohorts between 2004 and 2011. BMC Geriatr. 2016;16:115.

Paper 2

Gulla C, Flo E, Kjome R, Husebo BS. Implementation of collegial mentoring and systematic clinical evaluation in nursing home patients in a cluster randomized effectiveness-implementation clinical hybrid trial: Introducing a novel strategy for multidisciplinary medication review. Submitted 2017.

Paper 3

Gulla C, Flo E, Kjome R, Husebo BS. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. J Geriatr Cardiol. Accepted, 2018.

Papers and manuscripts are printed at the end of the thesis. Reprint was made with permission from BMC geriatrics.

Abbrevations and definitions

Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockers
ATC	Anatomical Therapeutic Chemical index
CDR	Clinical Dementia Rating scale
CI	Confidence interval
CMAI	Cohen Mansfield Agitation Inventory
CNPI	Checklist of Nonverbal Pain Indicators
COSMIN	COnsensusbased Standards for the selection of health status Measurement INstruments
COSMOS	Acronym for the RCT trial in Paper 2 and 3: COmmunication, Systematic pain assessment and treatment, Medication review, Organization of activities, and Safety
FAST	Functional Assessment Staging Tool
ICD-10	International Classification of Disease
ICPC	International Classification of Primary Care
MMSE	Mini Mental Status Examination
MOBID-2	Mobilization-Observation-Behaviour-Intensity-Dementia 2 Pain Scale
NPI-NH	Neuropsychiatric Inventory – Nursing Home version
NPS	Neuropsychiatric symptoms
PSMS	Physical Self Maintenance Scale
QUALID	Quality of Life In late stage Dementia
RCT	Randomized Controlled Trial
SD	Standard deviation
SEFAS	Centre for Elderly and Nursing Home Medicine
SHELTER	Services and Health for Elderly in Long TERm care trial
START	Screening Tool to Alert doctors to the Right Treatment
STOPP	Screening Tool of Older persons' Potentially inappropriate Prescriptions

Definitions

Deprescribing	Reducing drugs under close monitoring
Multimorbidity	Co-occurrence of multiple diseases
Nonagenarian	Person in his/her nineties
Octogenarian	Person in his/her eighties
On demand drugs	Frugs prescribed by a physician to be given if necessary
Polypharmacy	≥5 drugs used regularly or on demand
Psychotropic drugs	ATC-classes: Antipsychotics, anxiolytics, antidepressants, hypnotics, and anti-dementia drugs
Regular drugs	All drugs prescribed in a set schedule

Abstract

Background

Today's nursing home patients are old, fragile and suffer from multiple conditions. Consequently, they use on average seven different drugs each day. The total burden of these factors increases the vulnerability to drug related harm. The most common condition affecting nursing home patients is dementia, a disease that often renders the patients unable to express the harms and side effects of drugs. For this reason, we need to exhibit extra caution to avoid harming the patient.

Aim

This thesis aims to explore how to optimize prescribing for Norwegian nursing home patients. The focus is on two of the major drug groups contributing to polypharmacy: psychotropics and antihypertensives. I will also describe the method and implementation of the medication reviews we used in the COSMOS study.

Method

The thesis is based on a paper from an epidemiological study of three nursing home cohorts (Paper 1), and two papers from the COSMOS study (Paper 2 and 3). All patients included are 65 years or older and receive long-term care in Norway.

Paper 1: A cross-sectional study of 4 793 patients from 129 nursing homes. Using ordinal logistic regression, we explored the association between the use of multiple psychotropic drugs and neuropsychiatric symptoms, common conditions, function, and dementia.

Paper 2: A study on the development of the medication review process in the COSMOS study; an effectiveness-implementation cluster randomized clinical hybrid trial. The data is from the intervention group, N=297 patents. We describe the implementation by structured feedback on the process, barriers and promoters. Two researchers read the feedback, identified, and discussed the main messages.

Paper 3: A cluster-randomized study using the COMSOS method investigating whether cognitive status affected change in number of antihypertensive used, and

whether change in antihypertensives affected blood pressure or pulse. Data includes all patients using antihypertensives at baseline in the COMSOS study, N=295. The intervention group received a medication review with collegial mentoring and education in the COSMOS elements. The control group continued practice as usual. Mixed model analyses were used to compare the groups and investigate change over time for the patients at baseline, month four, and month nine. We used change in number of antihypertensive drugs used, systolic and diastolic blood pressure, and pulse as outcomes.

Results

Paper 1: 73% of the patients used psychotropic drugs and 41% used two or more. Antidepressants were used by 39%, 30% used sedatives, 24% used anxiolytics, 20% used antipsychotics, and 14% used anti-dementia drugs. There was a strong association between neuropsychiatric symptoms and use of multiple drugs. Females, younger patients, patients independent in daily living, and patients with a diagnosis of dementia also used more psychotropic drugs.

Paper 2: All intervention units in the COSMOS study conducted medication reviews with collegial mentoring during the first four months of the study and 92% of the patients received a medication review. Implementation facilitators were improved communication and enthusiasm towards the study and education. Barriers were lack of time, difficulties in involving the staff and physicians, and ethical dilemmas in relations to stopping treatment.

Paper 3: The patients used on average 9.2 drugs, and 1.6 antihypertensives each. Mean blood pressure at baseline was 128/71 mmHg, 9% had high pressure and 5% low pressure. Some 32% of the intervention patients had at least one antihypertensive reduced between baseline and month four, compared to 10% on the control patients. For patients with a reduction in antihypertensive drugs, the systolic pressure rose on average 14 mmHg between baseline and month four, but returned to baseline level by month nine.

Conclusion

The use of psychotropic drugs and antihypertensives is extensive among nursing home patients. Patients with dementia and neuropsychiatric symptoms receive more psychotropics. Dementia does not affect deprescribing of antihypertensives. Clinical medication reviews can lead to a reduction of antihypertensive drugs.

To implement a complex intervention, one needs to involve all staff and set aside time to implement the intervention. The implementation can lead to greater enthusiasm towards the work and improved communication between staff, physicians, patients and relatives.

Consequences

There is a need to improve the drug treatment for nursing home patients. By working together and using each other's skills and knowledge, we can reduce the use of drugs and focus on the right treatment for the individual patient. This thesis demonstrates a method that includes systematic assessment of symptoms and a clinical medication review with multidisciplinary teams and collegial mentoring.

Sammendrag

Bakgrunn

Dagens sykehjemspasienter er gamle, skrøpelige. De har mange sykdommer og får i gjennomsnitt sju legemidler hver dag. Samlet fører dette til at de er mer utsatt for legemiddelrelaterte skader. Den vanligste sykdommen blant sykehjemspasienter er demens, en sykdom som ofte gjør pasienten ute av stand til å fortelle om skadene og bivirkningene medisinene skaper. Vi må derfor være ekstra forsiktige for å ikke skade sykehjemspasientene.

Mål

Å undersøke hvordan vi kan forbedre bruken av to av de store legemiddelgruppene som bidrar til polyfarmasi; blodtrykksmedisiner og psykofarmaka. Jeg vil også beskrive metoden vi brukte i KOSMOS studien.

Metode

Alle pasientene i studiene er langtidspasienter i Norge, og er 65 år eller eldre.

Artikkel 1: En tverssnittstudie av 4793 pasienter som ser på sammenhengen mellom bruk av flere psykofarmaka og nevropsykiatriske symptomer, vanlige diagnoser, funksjon og demens. Vi brukte ordinal logistisk regresjon for å se på assosiasjoner.

Artikkel 2: Er en studie som ser på implementeringen av legemiddelgjennomgangen i KOSMOS studien, en effektivitets-implementering klyngerandomisert klinisk hybridstudie. Vi bruker kun data fra intervensjonsgruppen, n=297. Vi måler og beskriver implementeringen ved hjelp av strukturerte tilbakemeldinger på prosessen, hemmere og fremmere. Tilbakemeldingene fra personalet ble analysert av to forskere for å finne hovedtema.

Artikkel 3: En klynge-randomisert studie med KOMSOS metoden som undersøkte om kognitiv status påvirket endring i blodtrykksmedisiner og om endring i antihypertensiva påvirket blodtrykk og puls. Vi inkluderer alle pasientene som stod på blodtrykksmedisiner ved studiestart i KOSMOS studien, N=295. Intervensjonsgruppen fikk KOSMOS intervensjonen med legemiddelgjennomgang og

personalet på avdelingene fikk utdanning innen KOSMOS elementene. Kontrollgruppen fortsatte som før. Flernivå og longitudinelle analyser ble brukt for å sammenligne gruppene og se på endring over tid for pasientene ved start, fire og ni måneder. Vi brukte endring i blodtrykksmedisiner, systolisk og diastolisk blodtrykk, samt puls som utfallsmål.

Resultater

Artikkel 1 viser at 73 % av pasientene brukte psykofarmaka og 41 % brukte to eller flere samtidig. Antidepressiva ble brukt av 39 %, 30 % brukte sovemedisin, 24 % angstdempende, 20 % antipsykotika, og 14 % anti-demensmidler. Vi fant en sterk sammenheng mellom nevropsykiatriske symptomer og bruk av flere psykofarmaka. Kvinnene, de yngre, de med høy funksjon og pasienter med en demensdiagnose i journalen brukte også mer psykofarmaka.

Artikkel 2 viser at alle avdelingene i KOSMOS studien utførte legemiddelgjennomganger, og at 92 % av pasientene hadde én legemiddelgjennomgang i løpet av de fire første månedene av studien. Entusiasme, forbedret kommunikasjon og gleden av å lære ble rapportert som fremmere, mens manglende tid, vanskeligheter med å involvere alt personell og legene, og etiske dilemmaer rund å avslutte behandling var barrierer.

Artikkel 3 viser at 295 pasienter brukte blodtrykksmedisiner ved start. Pasientene brukte i snitt 9,2 legemidler og 1,6 blodtrykksmedisiner hver. Gjennomsnittlig blodtrykk ved baseline var 128/71 mmHg, 9 % hadde høyt blodtrykk og 5 % hadde lavt blodtrykk. Blodtrykksmedisiner ble redusert hos 32 % av intervensjonspasientene og hos 10% av kontrollpasientene. For pasienter hvor blodtrykksmedisiner ble redusert, så vi en økning i systolisk blodtrykk på 14 mmHg ved fire måneder, mens ved ni måneder var blodtrykket som ved start.

Konklusjon

Det er en utstrakt bruk av psykofarmaka og blodtrykksmedisiner blant sykehjemspasienter. Pasienter med demens og nevropsykiatriske symptomer får mest psykofarmaka. Kliniske legemiddelgjennomganger førte til en generell reduksjon i

forebyggende blodtrykksmedisiner. Det var ingen forskjell i nedtrapping av blodtrykksmedisiner om pasienten hadde demens eller om pasienten var kognitivt frisk.

For å få implementert komplekse intervensjoner må vi involvere alle ansatte og sette av tid til å implementere intervensjonen. Implementeringen kan føre til økt entusiasme for arbeidet og bedret kommunikasjon mellom ansatte, legene, pasientene og pårørende.

Konsekvenser

Det er et behov for å forbedre foreskrivningen til sykehjemspasientene. Ved å jobbe sammen og utnytte hverandres kunnskap og evner, kan vi redusere legemidler og fokusere på rett behandling til hver pasient. Denne avhandlingen fremmer en metode som inkluderer systematisk kartlegging av symptomer og kliniske legemiddelgjennomganger med tverrfaglig arbeid og kollegial støtte.

1. Background

1.1 Norwegian nursing homes

1.1.1 The nursing home

The definition of nursing homes varies from country to country. Sandford et al provide a fine example of this variation [16]. They polled experts in the field of nursing homes in 17 countries and found diversity in definitions ranging from "facilities giving extended medical care and rehabilitation" to "a place providing room and board". They also point out that the US definition of nursing homes includes advanced facilities, resulting in fewer patients with dementia in their cohorts. Despite these differences, most countries define long-term care as nursing homes outside the hospital, managing chronic medical conditions and providing around-the-clock help with activities of daily living.

Caring for the oldest old is an increasing challenge as the population is aging and more and more people develop dementia [17]. Dementia-related costs are responsible for 1.2% of the gross domestic product in high-income countries. Almost 50 million people are affected by dementia worldwide. The estimate for Norway is approximately 70 000 [18]. The population in Norway is 5 258 317; of these are 768 000 (14.6%) older than 67 years [19]. There are 31 000 beds in long-term care, and 3.2% of the population over 67 years are living in nursing homes. The percentage of people over 65 years old living in nursing homes in Europe ranges from 0.8% in Lithuania to 20% in Slovenia [20]. In Austria, the United Kingdom and the USA around 4% of the people aged 65 and older are in nursing homes

By law, every Norwegian citizen is entitled to nursing home services if this is deemed the only solution to give the patient necessary treatment and proper health and care services [21]. The municipalities decide whether the patient qualifies for long-term care. Most nursing homes are run by the municipalities. A small minority are run by non-profit organizations or commercial companies commissioned by the municipalities [22].

Long-term care consists of different units. Patients with dementia are known to express a high degree of NPS, like agitation, wandering, and psychotic behaviour [23]. Patients with dementia need smaller units and specialized care [24]. Specialized dementia care units have been around since the 80s, however, what they actually provide varies greatly [25]. In Norway, such units are small with four to 12 patients and admission requires a diagnosis of dementia [26]. Normal long-term care units do not require the patient to have dementia, and have no upper limit of patients per unit. The percentage of patients with dementia is high in normal long-term care units as well, where 79% of the patients are affected by dementia [27].

1.1.2 The providers of medical treatment and care

Physicians

The difference in service provided is reflected in the availability of physicians. An international survey of nursing homes in 30 countries found that only one-third of the countries had regular visits by a physician to the institutions [28]. In the USA, nursing home physicians are specialists with lengthy experience [29]. In Germany, on the other hand, the physicians are general practitioners for individual patients in the nursing home, and they have offices outside the nursing home [30]. In Norway, the medical care in the nursing homes is typically provided by general practitioners with visiting hours in the nursing home. Lately, as the Norwegian nursing homes have received more responsibility for patients after discharge from the hospitals, more physicians are working full-time in the nursing homes [31]. However, the newly discharged patients are often in short-term care, and these units are probably where most of the increase in physicians is seen. Until March 2017 there were no requirements for physicians working in nursing homes other than a medical degree [32]. After this new requirements of having, or being qualified under a specialization came in place, the Norwegian Medical Association recommends that physicians working in nursing homes should have one hour a week for every three long-term care patients, and one hour for every two patients in specialized units for patients with dementia [33]. This means that one full-time physician can provide for 60-90 patients. In Norway, 23% of the beds in nursing homes are for rehabilitation and

short-stays [19, 33]. These require one physician per 6 to 20 patients. Table 1.1.1 describes the situation for physicians in Norwegian nursing homes and the most conservative estimates on number of physicians (all short term beds are regular short-term patients, and no units specialize in dementia). According to these numbers, if we follow the standards set by the Norwegian Medical Association, there is a shortage of physicians in nursing homes.

Table 1.1.1 **Nursing home patients and their physicians in Norway, estimates and actual numbers**

Number of beds in nursing homes		**Recommended patients per physicians**	**Estimated need of full time equivalent physicians**	**Full time equivalent physicians working in nursing homes**
Total	*40 708*	*Not applicable*	*814*	*570*
Short term	9 303	20	465	Not known
long-term	31 405	90	349	Not known

Recommendations are based on the Policy note nb 8, 2012 from The Norwegian Medical Association.

Staff

Norwegian facilities are staffed by registered nurses, typically one per 10 patients, and one licensed practical nurse per seven patients [34]. Pharmacists are rarely employed by nursing homes. The nursing home staff's skills and knowledge varies across countries. The UK and USA have seen an increase in the use of advanced practical nurses in nursing homes [28]. These nurses are educated to work independently and provide more advanced treatment than regular registered nurses. In Norway, there is no tradition for use of these advanced nurses. However, in 2011, an education of advanced nurses (nurse practitioners) started at the University of Oslo.

There has been an increasing focus on the relationship between quality of care and staffing in nursing homes [35-38]. The publications focus on the numbers of different professions and personnel, and do not assess the knowledge and skills of the staff. The research has primarily been conducted in the USA, with only one study from Norway and one from Italy [35, 38]. A Norwegian group investigated the competence of nursing staff working in home care services or nursing homes [39]. A questionnaire was answered by 1016 nursing staff, and revealed that the nursing staff had competence in key areas of nursing. However, there was a lack of competence in

advanced nursing procedures, palliative nursing, patient observation, and nursing documentation. The researchers also found that registered nurses had more knowledge than the assistants did, and that nursing home staff had more competence than staff in home care services.

1.2 Patients in nursing homes

Permanent residency in a nursing home becomes more and more likely as we age; 11% of octogenarians and 30% of nonagenarians in Norway live in nursing homes [40]. The average age for patients in long-term care is 85 years in Europe and Norway [4, 41]. The majority of the residents are female and over 80% of patients have dementia [27].

1.2.1 Dementia

Epidemiology

The World Health Organization's International Classification of Diseases version 10 (ICD-10) classifies dementia as a mental and behavioural disturbance [42]. It is a chronic, debilitating disease leading to progressive decline in higher cortical functions like memory, thinking, calculation, learning capacity, orientation, judgement, and comprehension [42]. Increased mortality is also seen in people with dementia, and dementia is one of the leading causes of death in the world [43, 44]. It is estimated that median survival after a diagnosis of Alzheimer's or vascular dementia is four to seven years [45].

A study of 696 patients newly admitted to nursing homes in Norway found that 16.2% had no dementia [27]. Of the people diagnosed with dementia by the study, 71% had Alzheimer disease, 8% vascular dementia, 2% mixed dementia, 8% frontotemporal dementia, 4% Lewy body dementia, and 7% had other types of dementia. While 80%, of the nursing home patients had dementia when examined, only 56% of them had dementia as a diagnosis in their medical records [27]. At the same time, 6% of the patients not diagnosed with dementia had dementia in their

medical records. This suggests that diagnostics of dementia are limited and we need to critically appraise the diagnoses in the medical records.

Stages

A person suffering from dementia will go through different stages of cognitive impairment [46]. The progress is highly individual, however Reisberg (1984) described the development of Alzheimer disease as follows: In the early and mild stages, the person is still able to take care of herself. She will forget pieces of personal history and recent events and have reduced concentration. As the disease progresses to moderate dementia she will lose orientation to time, date, and place. She will remember the names of her closest relatives, but have difficulties dressing according to season and weather. In the severe stages of dementia she will lose the ability to go to the toilet, dress herself, and eventually the words will be lost. In end stage disease, she will not be able to walk, and swallowing difficulties are common. At this stage, she will also normally experience infections [46].

Neuropsychiatric symptoms

Dementia is closely connected with NPS, which is a range of different behavioural and psychological disturbances such as depression, apathy, hallucination, delusions, agitation, disinhibition, and aggression. These symptoms will affect virtually everyone with dementia at some point in their disease [47]. The symptoms have different prevalence rates during the course of the disease. For instance, depression and apathy are especially prevalent in the early stages of disease, while psychotic symptoms and aggression become more prevalent as the disease progresses [48]. Apathy, disinhibition, and irritability are the most prevalent symptoms in nursing home patients, and will affect three out of five patients over a four-year period [47]. Apathy and agitated behaviour are also the most persistent symptoms. These symptoms are burdensome for the patient and caregivers, and reduce the patient's quality of life [49, 50]. They are also main contributors to nursing home admission [51].

1.2.2 Other common conditions and multimorbidity

Although dementia is the most frequent disease in nursing homes [27], other diseases are also commonly seen. The Services and Health for Elderly in Long TERm care (SHELTER) study pooled data from 57 nursing homes in Israel and seven European countries [5]. They found that the patients had an average of two diagnoses each, with cardiovascular diseases on the top of the list: ischemic heart disease affecting 26%, stroke 22%, and heart failure 18%. Other frequent diagnoses in nursing home patients are diabetes (19% of the patients), and atrial fibrillation (21%) [52]. These diagnoses often occur together in the same patient. Each diagnosis in itself might not influence the patient too much. However, their co-occurrence, also known as multimorbidity, can cause considerable frailty for the patient [1]. Frailty reduces the threshold for when the patient becomes dependent on help, and minor illnesses or discomforts can result in reduced function.

Symptoms

All the diseases affecting the nursing home patients have a potential to cause a wide array of symptoms. Common symptoms include urinary incontinence (affecting 80% of patients) [53], faecal incontinence (40-67%) [53, 54], pain 30-60% [5, 53, 55], falls (9-50%) [5, 53], oedema (25%) [53], constipation (6-23%) [53, 56], dyspnoea (13-20%) [5, 53], and dizziness (15%) [5]. People with dementia have reduced ability to understand and communicate symptoms [46], and discomfort might be expressed as behaviours similar to NPS [57, 58]. Most of these symptoms can be treated or alleviated– when identified. An assessment of NPS should aim to clarify whether the symptoms the patient is expressing are a sign of progression of the dementia, a sign of unmet needs, or are they caused by pain or discomfort [59].

Assessment of symptoms

The most used tests for pain and NPS rely on the patients' ability to report symptoms [60, 61]. Since people with dementia are unable to grasp the content of abstract questions relating to feelings and time span, a proxy-rater with sound knowledge of the patient has to evaluate the patient [62]. The array of assessment instruments is as

varied as a bouquet of spring flowers. For example, there are at least twelve instruments used for assessment of pain in people in with dementia. Of these, three are translated into Norwegian; DOLOPLUS 2 scale [63], checklist of nonverbal pain indicators (CNPI) [64], and Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) pain scale [65]. The two former rate pain-related behaviours, while the latter rates pain related to active movements. CNPI and MOBID-2 can also be used to evaluate the treatment effect of analgesics [65, 66]. MOBID-2 is the only instrument available in Norway where pain can be located through five active movements. The same diversity of different scales is found for assessment of neuropsychiatric symptoms, and quality of life, and no one assessment tool is recommended over the others [67, 68].

Non-pharmacological treatment of neuropsychiatric symptoms

When the proper clinical investigations and assessment of NPS is done, we can identify, treat, and alleviate the conditions and meet otherwise unmet needs [69]. In treating NPS, non-pharmacological approaches should be tested before the initiation of drugs [70-73]. There is a wide variety of non-pharmacological interventions tested on NPS, ranging from person-cantered care, exercise, music, validation therapy, and reminiscence therapy. All these therapies impose a low risk of harm [74], and education of staff has the best documentation to improve the residents' and staffs' life [75].

1.3 Drugs in nursing homes

1.3.1 Demographics

The average nursing home patient use seven to eight drugs every day [5, 76] – as a result, the majority of patients are affected by polypharmacy. The most frequently administered drugs are laxatives, analgesics, antiulcer drugs, anticoagulants, antihypertensives, and psychotropic drugs [5, 76]. Over the past decade, there has been a shift towards more analgesic prescriptions, particularly for paracetamol and strong opioids [4]. Our research group might have contributed to this by focusing on

how pain treatment can alleviate agitation [77]. At the same time, the use of psychotropic drugs has increased, especially antidepressants, hypnotics, and anxiolytics are surging [78]. Antipsychotics are the only class of psychotropic drugs with a reduction in use.

1.3.2 Psychotropic drugs

Psychotropic drugs are mostly prescribed for NPS [69]. Antipsychotics are the second-line treatment for agitation and psychosis, and studies have shown that these symptoms go hand in hand with antipsychotic prescribing [79, 80]. Antipsychotics were discredited in the USA in 2005 due to increased mortality risk [81]. Therefore, antidepressants and anti-dementia drugs have received increasing attention in treatment of NPS [8]. A meta-analysis investigated the effect of psychotropic drugs on NPS in patients with Alzheimer disease [82]. The analysis revealed a positive effect on total burden of NPS for atypical antipsychotics and cholinesterase inhibitors (Table 1.3.1).

Table 1.3.1 **Effects of psychotropic drugs on NPS in patients with Alzheimer disease, results from Wang *et al.*, 2015**

Treatment	**Standard mean difference (95% confidence interval)**
Atypical antipsychotics vs placebo	-0.21 (-0.29, -0.12)
Cholinesterase inhibitors vs placebo	-0.12 (-0.23, -0.02)
Antidepressants vs placebo	0.01 (-0.35, 0.37)
Mood stabilizers vs placebo	0.96 (0.16, 1.76)
Memantine vs placebo	-0.12 (-0.27, 0.03)

Antidepressants and memantine did not affect NPS. The use of antipsychotics and cholinesterase inhibitors led to more dropouts and side effects than antidepressants and memantine [82]. The effect of antidepressants on depressive symptoms in people with dementia is also debatable [83]. Anti-dementia drugs show significant improvement in cognition for people with dementia, meanwhile, these effects are minor and the drugs have substantial side effects [84]. Discontinuation studies of antidepressants, antipsychotics, cholinesterase inhibitors, and sedatives show that these drugs can safely be discontinued under close monitoring [85-88].

Despite the limited effect and considerable adverse-events issues, the use of psychotropic drugs is high, with 70% of the nursing home patients using at least one, and 22% using a combination of psychotropics [78]. It is also remarkable that patients are prescribed these drugs for many years. A study investigated 1163 nursing home patients and their psychotropic drug use over time [89]. The residents were assessed at baseline, and after 12, 31, 52, and 72 months. Between any two assessments, the persistence for any psychotropic drug was over 50%, except for anti-dementia drugs where the persistence fell to zero. Change in symptoms between two assessments did not affect persistence [89].

1.3.3 Antihypertensive drugs

Hypertension is one of the major risk factors for stroke and cardiovascular disease [90], and cardiovascular diseases are the top causes of death in the world [44]. Treating hypertension significantly reduces the risk of these diseases and death [90]. The European guidelines on management of hypertension state that antihypertensive treatment is recommended for fit elderly over 80 years if systolic blood pressure is 160 mmHg or more [90]. For frail elderly, they leave the decision to the treating physician based on monitoring and effects of treatment. All of the antihypertensives are recommended in the treatment of hypertension; however, diuretics and calcium antagonists are preferred in isolated systolic hypertension. The most used drugs with antihypertensive effects are diuretics, angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), beta-blockers, and calcium channel blockers [5].

The association between treatment and favourable outcomes in the frailest and oldest patients is contradictory. The studies investigating the effect of antihypertensives in people over 80 have excluded nursing home patients and people with dementia [91, 92]. A Swedish study on 406 nursing home patients found that low, rather than high blood pressure, was associated with increased mortality [52]. Between 7 to 13% of the nursing home patients have a systolic pressure above 160 mmHg [52, 93], but 45% receive antihypertensives [94]. Antihypertensive treatment can cause

hypotension. A cross-sectional study of 5066 patients aged 80 years and older treated for hypertension; found that 34% had hypotension [95]. The most disturbing result from this study was that 59% of the hypotension identified with ambulatory blood pressure monitoring was not detected by office measures.

1.3.4 Why is drug treatment difficult?

The range of drugs the patient should use according to the disease-specific guidelines when he or she have multimorbidity is wide [96]. This can cause polypharmacy, an individual risk factor for side effects, inappropriate drug use, and hospitalization [3].

A main point is that the guidelines are disease specific, and do not address the multimorbid nature of the nursing home patients [97]. A second core point is that the research on drug effectiveness excludes the elderly and frail [98]. If we do not consider these two factors when treating the frail, multimorbid elderly – we can cause

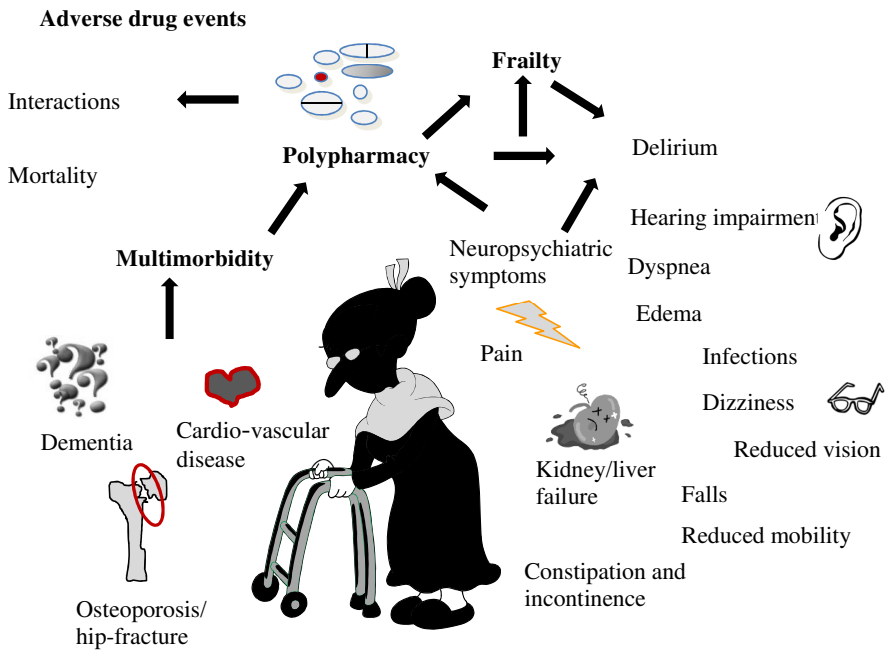

Figure 1.3.1 **Why is prescribing difficult? Factors influencing prescribing and results of prescribing for nursing home patients**

serious harm. An overview of factors complicating prescribing is given in Figure 1.3.1.

Increased succeptibility to side effects

Old people, and especially patients suffering from dementia, are more susceptible to side effects than younger patients [99, 100]. These side effects include falls, fractures, delirium and even death [100-102]. Delirium is an acute change in cognitive status, with the hallmarks fluctuation in symptoms and inattention [103]. It increases mortality but is preventable in 30-40% of the cases. Predisposing factors for side-effects are present in the average nursing home patient: dementia, functional impairment, multimorbidity, old age, and sensory impairment.

Phamacokinetic and pharmacodynamic changes

As the body ages, internal organs and cells alter [104]. These changes lead to pharmacokinetic and pharmacodynamic changes. Important pharmacokinetic changes are reduced kidney function and altered fat-to-muscle ratio. A reduced kidney function leads to excess concentration of drugs or metabolites execrated by the kidneys, like the increase seen of the active metabolites of morphine [105]. The increase in body fat inflates the volume of distribution for fat-soluble drugs like benzodiazepines and escalates their half-life. Pharmacodynamic changes might increase or decrease sensitivity to drugs, and cause unpredicted adverse events [104].

Interactions

Adverse events can also be caused by drug-drug interactions or drug-disease interactions [106]. A drug-drug interaction is an alteration of the effect of one drug due to another drug, while a drug-disease interaction is when a drug prescribed for one condition exacerbates another pre-existing, chronic condition.

Known drug-drug interactions can be identified by imputing drugs in interaction databases. In Norway the database is readily available in apps and online [107, 108]. The database only compares pairs of drugs, and is not capable of estimating the effects of a combination of more drugs. Another weakness is the poorer representation of pharmacodynamic interactions in the database.

Drug-disease interactions require a clinical understanding of the patient and pharmacological understanding of the drugs [106]. The risk of interactions increase with the number of drugs prescribed, and when a patient receives eight drugs, the average number of interaction is one [109].

1.4 Interventions in nursing homes

A search on pubmed.gov for clinical trials in nursing homes reveals 2186 trials published before January 2016 (Figure 1.4.1). During the past decade there have been

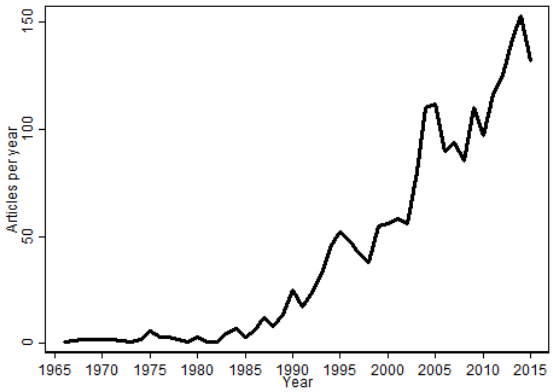

Figure 1.4.1 **Published articles in pubmed.org on clinical trials in nursing homes**

over 100 published trials concerning nursing homes each year. Dementia care, drug use, and infection control are major topics of these studies. The interventions often involve multiple professions and several modes of delivery of the intervention [9].

The complicated nature of nursing home patients makes “one-size-fits-all”-solutions hard to design. Therefore, one can either aim a specific intervention at a small selected group of patients or create a more general approach for different patients and units. The former choice is often tested by randomized controlled trials, the gold standards and backbone of evidence based medicine [110]. The latter choice often calls for complex interventions. These are interventions with many organizational levels involved, multiple different actions, multiple outcomes, and a need for

flexibility in tailoring the intervention [15]. The planning, conductance, and reporting are somewhat different between the two types of trials.

By nature, the complex interventions involve many organizational levels and different interventions. The development of this type of study requires identification of the existing evidence –regarding both the interventions and how to evaluate them [15]. Another aspect is to use the evidence and theory to develop a theoretical understanding of what type of change we want, and how change will occur [15]. The next step is to develop a model for the intervention process and pilot it. The pilot should investigate key parts that might need improvement.

Conducting complex studies is more flexible than performing traditional randomized controlled trials. The flexibility makes it possible for the researchers to adjust the intervention towards the needs of the different participants [15]. Scientific reporting should therefore be done on all the areas in the process: development, evaluation, testing, and implementation. This requires, in addition to the traditional reporting of primary endpoints, a sound description of the method, implementation strategies, and the extent to which the intervention was implemented.

These aspects are often lacking, and data on implementation is only reported in five of the 14 studies in the review by Forsetlund [12]. The five studies that do report on implementation do this to a varying degree. This makes the interpretation of study results difficult. We do not know if the intervention succeeded or failed because of the (in)effectiveness of the implementation or (in)effectiveness of the interventions. Complex interventions are notoriously difficult to implement, and translating the evidence from these studies into practice is a slow process [111]. Some of the hindrances include lack of economic incentives, lack of staff knowledge, understaffing and high turnover rates among staff [111].

1.5 Methods of improving prescribing

1.5.1 Optimal prescribing

There are two main approaches for assessment of prescribing in the elderly; using explicit criteria or implicit measures that are judgement-based [112]. Some of the most used explicit criteria internationally and in Scandinavia are listed in Table 1.5.1 [113-119]. The table shows that most of the criteria are intended for the general older population, not the nursing home population. There is also a huge variability of the number of criteria in each list. All, except the PRISCUS list [116], include diagnose specific advices as well as general advice on drugs. The explicit criteria have been

Table 1.5.1 **Explicit lists for prescribing to older patients**

Author (year), country	**Name**	**Number of criteria**	**Intended for**
American Geriatric society expert panel (2015), US	Beers Criteria for Potentially Inappropriate Medication Use in Older Adults	86	Ambulatory, acute, and institutionalized settings of care for populations aged 65 and older in the United States, with the exception of hospice and palliative care
O'Mahony (2015), Ireland	STOPP/START criteria for potentially inappropriate prescribing in older people: version 2	STOPP: 80 START: 34	Patients aged 65 and older who is not clinically in the end-of-life
Laroche (2007), France	French consensus panel list	34	French population aged 75 years and older
Holt (2010), Germany	PRISCUS	30	Elderly patients
Pazan (2016), Germany	FORTA	240	Elderly patients
Swedish National Board of Health and welfare (2010), Sweden	Swedish national indicators	20	Elderly aged 75 years and older
Nyborg (2015), Norway	NORGEP-NH	34	Nursing home patients

criticised because they do not take into account co-morbidity or the patient's wishes [112].

The implicit criteria are judgement-based, and often focus more on the patient than on the individual drug – this is an individual process and the outcome will vary between physicians [112]. The most used implicit criterion is the Medication Appropriateness Index, consisting of 10 questions for every drug prescribed [120]. These 10 questions concern indication, correct medication for the indication, dosage, correct direction, drug-drug interactions, drug-disease interactions, duplicate drugs, duration, and cost of drug. The implicit criteria are time consuming to apply and are demanding for the clinician to use [112].

Two Swedish studies investigate the sensitivity and specificity for the different criteria to identify suboptimal prescribing compared to a gold standard in 200 hip fracture patients aged 65 and older [121, 122]. The results are presented in Table 1.5.2 [121, 122]. By sensitivity they meant how many of the patients identified by the gold standard as having inappropriate prescribing were also identified by the criteria. Specificity was defined as the proportion of patients with appropriate drug treatment according to a gold standard, not identified by the criteria. The gold standard was

Table 1.5.2 **Comparison of different indicators to assess prescribing quality in hip-fracture patients over 65 years**

Indicator	**Patients identified to have inappropriate treatment (N=200)**	**Sensitivity**	**Specificity**
Gold standard	71%	NA	NA
French consensus panel list	27%	0.33 (0.26-0.41)	0.88 (0.77-0.94)
PRISCUS	22%	0.29 (0.22-0.37)	0.97 (0.88-0.99)
Swedish indicators	41%	0.51 (0.43-0.59)	0.83 (0.72-0.91)
Polypharmacy (≥5 drugs)	75%	0.86 (0.80-0.92)	0.53 (0.41-0.65)
Excessive polypharmacy (≥10 drugs)	25%	0.32 (0.25-0.40)	0.93 (0.82-0.97)

defined as a screening with the START/STOPP criteria [123] and evaluation of the identified problems as clinically relevant or not by a geriatrician and a general practitioner. One striking aspect is the ability of polypharmacy to detect poor prescribing, underlining the connection between polypharmacy and inappropriate treatment.

1.5.2 How to optimize prescribing?

Combining implicit and explicit criteria can reduce the drawbacks with both approaches. This can be done in multidisciplinary medication reviews or case conferences. Five recent reviews analyse the effects of interventions aimed at improving prescribing in nursing homes (Table 1.5.3) [9-12, 14]. These reviews include a total of 39 studies on how to improve prescribing and outcomes on such trials.

Table 1.5.3 **Reviews on methods to optimize prescribing in nursing homes**

Author (year), included studies	**Focus**	**Inclusion and exclusion**	**Conclusion**
Alldred, D.P. (2016), N=13	Effect of interventions to optimize prescribing	*Inclusion:*1) RCT, 2) 65 and older in NH *Exclusion:* 1) Single medical condition, or specific drug class/drug, 2) main focus to reduce medication errors	Huge variability in studies, low certainty of evidence for identification and resolution of drug-related problems and improvements in appropriateness of drugs.
Wallerstedt (2014), N=12	If medication reviews reduce mortality and hospitalization	*Inclusion:* 1) RCT or CT, 2) NH residents, 3) intervention using medication reviews with outcomes hospitalization or mortality *Exclusion:* 1) Not written in English, Swedish, Norwegian, or Danish, 2) Medication review only on specific drug classes or condition	Medication reviews does not reduce hospitalizations or mortality.
Forsetlund, L. (2011), N=20	Effects of interventions to reduce potentially inappropriate prescribing or use of drugs	*Inclusion:*1) Systematic reviews of RCT or and/or primary RCTs, 2) Interventions aimed to reduce potentially inappropriate use of drugs, 3) primary outcome assessed with prescribing criteria or specific drugs were targeted, 4) secondary outcomes: falls, mortality, hospital admissions, or physical restraints *Exclusion:* Not in Norwegian, Swedish, Danish, Finish, English, or German	Best evidence for educational approaches for improving prescribing. Lack of reporting of implementation.
Loganathan, M. (2011), N=16	Effects of interventions to optimize prescribing	*Inclusion:* 1) RCT or CT, 2) NH residents with mean age ≥65, 3) evaluated the effect of an intervention on prescribing, aimed at improving appropriate prescribing or reducing inappropriate prescribing, 4) published between 1990 and 2010 in English	Education best studied and showing improvements in prescribing.

Table 1.5.3 **Continued**

Author (year), included studies	**Focus**	**Inclusion and exclusion**	**Conclusion**
Marcum Z.A. (2010), N=18	Analyze RCTs on improvement suboptimal prescribing	*Inclusion:* 1) RCT, 2) residents 65 or older, 3) had a process measure outcome for quality of prescribing or a distal outcome measure for drug-related adverse patient events	Few studies investigated patient's health or adverse events, weak evidence for improvement.
Verrue C.L.R. (2009), N=8	Improvement of quality of prescribing by pharmacist Key elements for successful intervention by pharmacist	*Inclusion:*1) Involved a pharmacist, 2) took place in NH, 3) residents 65 or older, 4) included residents with a range of diseases *Exclusion:* 1) Not in English	Mixed results on effectiveness, studies have many limitations

CT: controlled trials, NH: nursing home, RCT: randomized controlled trials

The interventions used by the studies identified in the reviews are listed in Table 1.5.4. Twenty-one of 39 studies use multicomponent approaches. Education was by far the most frequently used intervention. Education was aimed at the staff and/or physician, and involved teaching sessions, workshops, education material, or combinations of these. The medication reviews in 12 studies were performed by the pharmacist, in seven by a multidisciplinary team, and in three by someone other than a pharmacist. In ten of the studies where the main prescriber was not involved in the medication review, he or she was present in in case conferences. The other studies gave written feedback to the main prescriber, without the possibility of discussing the cases.

Table 1.5.4 **Interventions used for optimizing prescribing**

Intervention	**Number of studies N=39**
Multicomponent	21
Education	
Staff	22
Material	8
Medication review	
Pharmacist	12
Multidisciplinary	7
Not multidisciplinary, performed by other profession than pharmacist	3
Case conferencing	10
Computer program	5
Other	6

The main conclusions of the reviews (Table 1.5.3) are that the studies are diverse and the effects are minor. However, there is best evidence for the educational approaches to improve the quality of prescribing. The ideal mode of delivery or intensity is still not known [75]. A review from 2013 on multidisciplinary interventions in nursing homes found that interventions involving multidisciplinary team meetings, the patient's physician, and a pharmacist were the most successful [124].

Deprescribing and person-centered care

There is an emerging focus on the term *deprescribing* as a way to optimize prescribing for the elderly [125, 126]. There is no clear definition of this term, and

Reeve et al. identified characteristics of definitions across 37 publications [125]. These are presented in Table 1.5.5

Despite the lack of a clear definition, deprescribing is now an accepted term and is increasingly used when appropriateness of drugs is considered [125]. Another emerging term regarding long-term care is Person-Centred Care. The American Geriatric Society tasked an expert panel with defining this term and decided on "(the) individual's values and preferences are elicited, and, once expressed, guide all aspects of their health care, supporting their realistic health and life goals" [127]. This is also described as a process with clearly defined outcomes, multidisciplinary work and continuous education. These two terms go hand in hand and their intent is present in most studies focusing on optimizing prescribing.

Table 1.5.5 **Characteristics included in definitions of deprescribing identified by Reeve et al (2015)**

Characteristics of deprescribing	**Number of studies that use the characteristic in their definition**
Stop, cease, withdraw, discontinue, remove	35
long-term use, potentially inappropriate drugs	18
Structured, process	13
Planned, supervised, judicious	11
Multiple steps	7
Dose reduction, substitution	7
Defined outcomes	5
Taper	4

1.6 Rationale of the thesis

From the above paragraphs, we can conclude that to improve prescribing we should educate the staff, include the physician and a pharmacist, and use multidisciplinary team meetings. To evaluate the patient's many symptoms and diagnoses we need a holistic approach taking all the elements in Figure 1.3.1 into account. This would require a complex intervention; hence, the development of the method needs to be addressed, as well as the implementation process and the primary outcomes.

2. Aims of the studies

The aim of this thesis has been to examine how to optimize prescribing for two of the major drug groups contributing to polypharmacy: antihypertensives and psychotropics. I also wanted to describe the method and implementation of the medication reviews in the COSMOS study. This has been achieved by performing one cross-sectional study (Paper 1), one method development and implementation process evaluation (Paper 2), and one effectiveness-implementation cluster randomized clinical hybrid trial (Paper 3), resulting in three papers. Their individual aims were:

Paper 1

Investigate the use of psychotropic drugs and the patient characteristics associated with the use of multiple-psychotropic drugs.

Paper 2

Describe a novel implementation strategy for a multidisciplinary medication review and report:

- How did nursing home staff receive the intervention?
- To what degree was the medication review implemented successfully?
- What are the barriers and facilitators for implementing multi-disciplinary medication reviews in nursing homes?

Paper 3

To investigate how a systematic medication review supported by collegial mentoring affected the use of antihypertensives. Secondary objectives were to assess associations between blood pressure at baseline and changes in antihypertensive drugs, and describe the effects of changes in therapy on blood pressure after four and nine months.

3. Methods

3.1 Overview of the papers

All papers included only patients living in Norwegian long-term care units. We recruited the units first, and then all the patients in the units were screened for eligibility. Patients had to be 65 years or older, and have stayed in the unit for at least two weeks before first assessment. Dying patients were excluded. Registered nurses in the units used validated instruments for people with dementia to obtain data on clinical and psychological status. The patient's records provided information on prescribed drugs, diagnoses, and demographics. An overview of design, number of patients, inclusion, and exclusion criteria is shown in Table 4.1.1. Paper 1 is based on data that was collected from 2004-2011 [128-130]. Papers 2 and 3 are based on the COSMOS study.

Table 4.1.1 **Overview of papers**

Paper	Design (study)	Inclusion and exclusion criteria	Number of patients
1	Cross-sectional (Selbaek 2007, Kirkevold 2009, Helvik 2015)	Inclusion • At least a two-week stay in long-term care • ≥65 years Exclusion • Dying	4739
2	Method development and implementation process evaluation (COSMOS)	Inclusion • At least a two-week stay in long-term care • ≥65 years Exclusion • Dying • Control group patients • Active schizophrenia	297
3	Effectiveness-implementation cluster randomized clinical hybrid trial (COSMOS)	Inclusion • At least a two-week stay in long-term care • ≥65 years • Use of antihypertensives at baseline Exclusion • Dying • Active schizophrenia	295

3.1.1 Assessment instruments used in the papers

People with dementia have reduced abilities to express pain and discomfort. They are reliant upon evaluation from others to be treated correctly. In the papers, we used a number of instruments validated for people with dementia. Only nurses having daily contact with the patients answered the instruments. All nurses received at least four hours of training before using the instruments. The researchers performed all the Mini Mental Status examination (MMSE). The following section contains a short description of the instruments used in the papers and Table 3.1.2 indicates how the instruments were used in the individual papers.

Table 3.1.2 **Overview of the use of instruments in the papers**

Instrument	Paper 1	Paper 2	Paper 3
MMSE		D, MR	D, P, MR
FAST		D, MR	MR
CDR	D, P		
NPI-NH total	D, P[1]	D, MR[2]	MR[2]
NPI-NH psychosis: Delusions and hallucination	P		
NPI-NH affective symptoms: Depression and anxiety	P		
NPI-NH agitation: agitation and irritability	P		
CMAI		D, MR	MR
Cornell		D, MR	MR
MOBID-2		D, MR	MR
PSMS	D, P	MR	MR
QUALID		MR	MR

D: used in the demographic section, MR: instrument used in medication reviews, P: Predictor
[1]Includes the 10 items: Delusions, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviour. [2]Includes the 12 items: Delusions, hallucination, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behaviour, and eating disturbances.

Cognition

Mini Mental Status Examination – MMSE

MMESE tests cognitive function by asking the patient 30 questions in the domains of orientation to time, orientation to place, registration, attention and calculation, recall, language, repetition, and complex commands [131, 132]. The answers are scored *correct* (1) or *wrong* (0), range 0–30. Lower scores indicate lower cognitive function. Normal cognition was defined as 26–30, mild dementia: 21–25, moderate dementia 11–20, severe dementia <11 [133].

Functional Assessment Staging – FAST

FAST stages cognitive function from normal to severe dementia [134]. Functioning is divided into seven major levels. A nurse marks the level that best fits the patient's functional status. Normal cognition was scored as 1–2, mild dementia as 3–4, moderate dementia as 5, and severe dementia as 6–7. The instrument has good validity and reliability [135].

Clinical Dementia Rating scale - CDR

CDR rates cognitive function from normal to severe dementia [136]. The test covers the domains memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The score goes 0 to 3, 0: no cognitive impairment, 0.5 questionable cognitive impairment, 1: mild dementia, 2: moderate dementia, 3: severe dementia. It is reliable and valid in diagnosing dementia [136-138].

Neuropsychiatric symptoms

Neuropsychiatric Inventory- nursing home version – NPI-NH

NPI-NH assesses neuropsychiatric symptoms in the twelve domains delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviours, night-time behaviours, and eating disturbances [139]. Each domain is scored on frequency (*absent* to *daily*; 0–4), and intensity for the patient (*mild* to *severe*; 1–3). These scores are multiplied to a sum score of 0–12 for each item. The NPI-total is a sum of the scores for each domain. It has good validity and reliability [140].

Paper 1 only uses the first 10 domains in the sum score, excluding nighttime behaviours and appetite since these items were added to the instrument at a later time. As such, the maximum score is 120. Paper 1 also uses sub-syndromes constructed from a factorial analysis of the NPI-NH scale [141]. In these, two and two domains are joined to create sub-syndromes: agitation (agitation and irritability), affective symptoms (depression and anxiety), and psychosis (hallucinations and delusions) [141].

Papers 2 and 3 use all twelve domains when calculating the sum score. Paper 2 also uses a cut-off score of four or more on an individual item as a clinically significant symptom.

Cohen-Mansfield Agitation Inventory – CMAI

CMAI investigates 29 agitated behaviours in the domains aggressive behaviours, physical non-aggressive behaviours, verbally agitated behaviours, and hiding and hoarding [142]. The items are scored on frequency (*never* to *multiple times an hour*; 1–7), sum score range: 29–203. In Paper 2, agitation was defined as a score of 39 or more. The instrument is reliable and valid to assess agitation in nursing home patients [142].

Cornell Scale for Depression in Dementia – Cornell

Cornell assesses depression through 18 questions in the domains mood, behavioural disturbances, physical signs, cyclic function, and ideational disturbances [62]. The items are scored *absent* to *severe* (0–2) and summed to give a sum score with a range from 0 to 38. In Paper 2, depression was defined as ≥8. Cornell is reliable and valid for assessing depression among institutionalized patients with and without dementia [143].

Other assessment instruments

Mobilization-Observation-Behaviour-Intensity-Dementia Pain Scale - MOBID-2

MOBID-2 measures pain intensity in five standardized, guided movements, and in five domains related to internal organs, head and skin in the last week [144]. Each item is scored from 0 to 10 (*no pain* to *worst imaginable pain*). A total pain score is based on the worst pain experienced in the 10 domains, ≥3 signifies a need for pain treatment. The instrument has good validity and reliability for assessing pain in people with dementia; it is also responsive to detect change in pain after adjusting treatment [65].

Physical Self-Maintenance Scale – PSMS

PSMS assesses personal activities of daily living in the areas toileting, feeding, dressing, grooming, physical ambulation, and showering [145]. The items are scored

based on whether the patients are able or unable to do the activity (0-5). A higher score signifies more dependency. It has good reliability and validity for assessing function in older people [145].

Quality of Life In Late-stage Dementia – QUALID

QUALID assesses quality of life with 11 questions about to what extent the person smiles, appears sad, cries, has facial expression of discomfort, appears physically uncomfortable, verbalizes in a way that suggests discomfort, is irritable or aggressive, enjoys eating, enjoys touching/being touched, enjoys interacting with others, and appears calm and comfortable [146]. Each item is scored from 1 to 5. Lower score indicates higher quality of life. QUALID is a reliable and valid tool to measure quality of life in people with dementia [147].

3.2 Paper 1

3.2.1 Participants

This study included three nursing home cohorts from 2004 [128], 2007 [129], and 2011 [130], including altogether 129 nursing homes throughout the country. Table 3.2.1 gives an overview of the included cohorts.

Table 3.2.1 **Overview of the three cohorts in Study 1**

Cohort	Aim	Nursing homes	Patients
2004	Investigate the relationship between neuropsychiatric symptoms and psychotropic drug use at different stages of dementia	26 NH from 18 municipalities	1137
2007	Examine the practice of concealing drugs in food and beverages	63 NH from south eastern Norway	1879
2011	Follow-up of the 2004 investigation	63 NH	1723

NH: Nursing home

3.2.2 Outcome and analyses

The outcome in Paper 1 was use the of psychotropic drugs. Psychotropic drugs were defined as antipsychotics (N05A), anxiolytics (N05B), sedatives (N05C), antidepressants (N06A), and anti-dementia drugs (N06D) according to the Anatomical Therapeutic Chemical Index (ATC) classes [148]. The term psychotropic drugs is not uniformly defined across articles, partly due to different classification systems of drugs across countries, the introduction of new drugs (like cholinesterase inhibitors), and differences in outcomes investigated. As we wanted to investigate the relationship between psychotropic drugs, dementia, and NPS, drugs treating these conditions were included.

The use of three or more psychotropics in elderly has been defined as inappropriate by Swedish and Norwegian prescribing criteria [149, 150]. The patients were therefore divided into four groups according to how many regular psychotropic prescriptions they used; zero, one, two, and three or more.

The ordinal nature of the outcome made it necessary to use ordinal logistic regression when investigating associations. As explanatory variables, we used the patient-related factors thought to have the greatest influence on psychotropic drug use: cognitive status, degree of neuropsychiatric symptoms, polypharmacy, and other diagnoses.

3.3 Paper 2

Paper 2 uses data from the COMSOS trial [151]. COSMOS was a four-month cluster randomized implementation-effectiveness clinical hybrid trial (Figure 3.2.1). The main aim was to improve quality of life for the patients and reduce NPS. The trial was complex with 67 nursing home units, five different interventions, and multiple meetings between the researchers, staff, and patients. The nursing home units came from seven municipalities in Norway: Askøy, Bergen, Bærum, Kvam, Sarpsborg, Sund, and Øygarden.

I joined the study just when ethical approval was received. The research team consisted of project manager Bettina S Husebø (BSH), postdoctoral fellow Elisabeth Flo and Irene Aasmul (IA) and I as PhD candidates. Together we recruited nursing homes, designed and finished the educational material, and finalized the intervention. We piloted the intervention with four small municipalities and subsequently refined the data collection method and medication reviews based on pilot experiences.

The main study was executed in Eastern and Western Norway. IA and I, together with two medical students (Torstein Habiger and Tony Elvegaard), collected all the data and performed the routine follow-up of all the units including phone calls to the units every second week in the first four months of the study. I organized the medication reviews with the intervention units, and BSH and I participated in them together with the physician and staff from the units. IA and I also planned the midway seminars, and I led two out of five of these sessions.

The study is described in detail in the published protocol [151]. This section will give an overview of the five COSMOS elements.

The complex design with five interventions and all personnel involved in patients' treatment was chosen as single-item interventions and has displayed minor effects (Table 1.5.3). The goal was that interventions would reinforce each other.

Each nursing home patient lives together with other patients in a unit. The patients in one unit are served by the same staff and physician. Since the intervention was given

to the nurses and physicians, it was reasonable to believe that the change in one patient was not independent of the other patients in the unit [77]. This dependency requires a randomization of the units (clusters) [152]. The clustered nature of the patients also requires statistical analyses taking into account that the observations are not independent. The measures were also repeated over time, which also has to be considered when choosing statistical methods. This is covered by using hierarchical repeated measure models, where patients are nested within units [153].

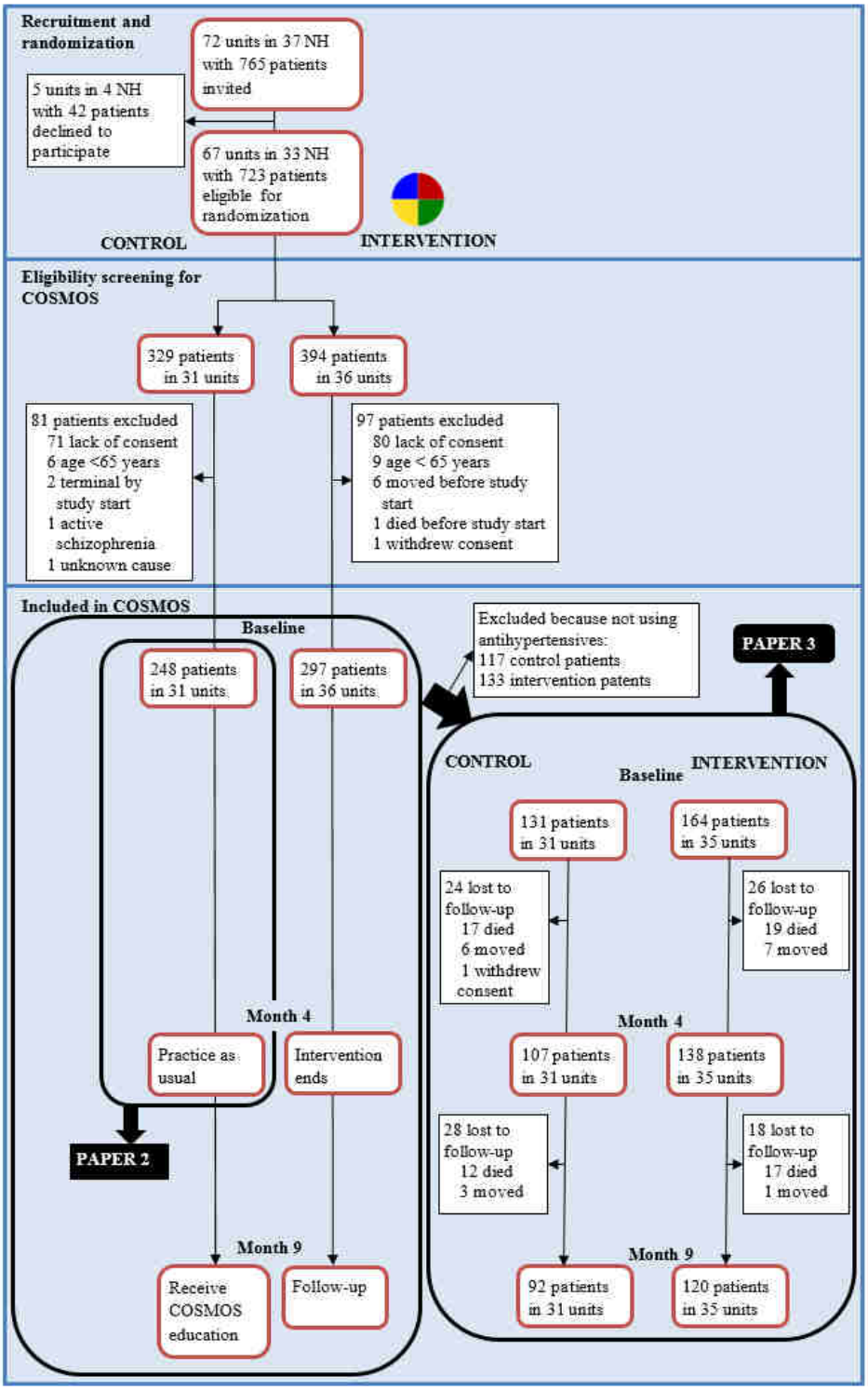

Figure 3.3.1 **Flow chart of the COSMOS study and description of the populations involved in Papers 2 and 3**

The interventions

The COSMOS trial tested a complex intervention consisting of five subsets of interventions. The reasoning was that each single intervention is dependent upon the other interventions to have maximum effect. It is not ideal to perform medication reviews without knowing what the patient and relatives want and believe. Removing drugs without a plan for following up the changes, especially removing psychotropics without giving proper individualized activities may increase suffering. To assess whether the pain treatment the patients received is adequate we need a valid measure of pain. To give individualized activities and set the right treatment level, it is essential to talk with the patient and relative about their beliefs and wishes. So, even though the two included papers from the COSMOS trial focus on medication reviews and drug use, the results are dependent on the whole COSMOS intervention.

Communication

In the communication section, the focus was on Advance Care Planning. This is a continuous process of communication and decision-making with the patient and relatives, where we address the patient's health and approaching death. Practical challenges in levels of care and ethics are considered and discussed before the patient becomes critically ill [154]. The nurses in the unit were supposed to have these conversations with the patient and relatives at least quarterly, and involve the physician when necessary.

Systematic pain assessment and treatment

In this section, we trained the staff in using MOBID-2 as a tool to detect and follow pain in their patients. By using a validated tool for people with dementia, they were able to detect over- and under-treatment. The body map on the MOBID-2 also visualized where the pain was, and enabled specific measures to reduce this pain. For instance, we found a patient in pain when lying on the left side and the left side was facing the wall when the patient was in bed. A morning routine involving washing and dressing the patient in bed would be better for the patient if the right side faced the wall. The staff and physicians were also trained in the Stepwise Protocol to Treat Pain [55] to optimize pain treatment. The goal was to assess all patients using

MOBID-2 at least two times a year, if the patient's behaviours changed, before initiation of pain treatment, 2–4 days after initiation, and after 8–12 weeks of treatment.

Medication review

In this section, we trained the nurses to assess the patients for pain, cognitive function, and neuropsychiatric symptoms. The staff and physicians received training on effects and side effects of drugs and how to assess effectiveness. We implemented multidisciplinary medication reviews with collegial mentoring. The physician and nurses from the unit participated together with the researchers (BSH and CG). We used the information from the assessments, medical records, lab tests, and clinical assessment. To support decisions the START/STOPP 2 [114], an online interaction database [107], the Norwegian Medicines Agency's checklist for medication reviews [155], and a list of anticholinergic drugs adapted from Duran et al [156] were used. The patients were to have a medication review twice a year, if their medical condition changed or if they were discharged from the hospital.

Organization of activities

By law, all Norwegian nursing home patients are entitled to have individualized activities [26]. This is because activities can increase quality of life, improve mood and reduce NPS. Activities should always be considered before initiation of psychotropic drugs and must be adapted to the patient's individual interests and abilities. The nursing home staff were taught the importance of activities, and given tools to map the individual activities for each patient based on preferences, interests, and physical and cognitive capabilities. The goal was for each patient to have an individual plan of activities with at least 1.5 hours a week of activities. If the patient received 1.5 hours a week at the start of the study, we aimed to increase the activities by 20%.

Safety

This is an overarching theme of the study. The elements in COSMOS are basic elements that should be covered for every nursing home patient. By using a system

that ensures that the focus is on these areas every fourth week, and document the measures, we enhance safety for the patient.

3.3.2 Participants

We included 36 intervention units with 297 patients. We also evaluated the COSMOS ambassadors (N=73) and physicians (N=21) responsible for the patients.

3.3.3 Outcomes and evaluations

The intervention process

This paper aimed to describe the intervention process. The method section of this paper was therefore extensive and resulted in the figure developed in the paper (Figure 6.3.1).

Evaluation of the implementation

We assessed the degree of implementation by using a log of activities for each patient. We asked five questions every fourth week through first four months of the study. The questions were:

- Has the patient had at least one medication review?
- Are there indications on each drug?
- Has the patient and/or relative been informed about change?
- Have any drugs been reinstated after pause?
- Are changes in patient health documented?

The barriers and promoters relative to implementation came from the midway seminar feedback, open-ended questions at each time-point in the patient logs, and feedback during the medication reviews. The feedback was read through by two researchers individually and “main messages” were identified. These were compared and discussed with all the researchers until consensus was reached.

3.4 Paper 3

3.4.1 Participants

We included the 227 patients from 35 units using antihypertensive drugs at baseline. The antihypertensive drugs were defined as the five most used groups with hypertension as a major indication in the Anatomical Therapeutic Chemical Index (ATC) [148]. These groups were high ceiling diuretics, beta-blockers, plain angiotensin II antagonists, plain angiotensin-converting-enzyme inhibitors, and calcium channel blockers with mainly vascular effect. Diagnoses were coded according to the International Classification of Primary Care (ICPC).

3.4.2 Outcomes and analyses

The primary outcome variable was the use of antihypertensive drugs defined as the number of antihypertensives the patients used at each time point. We considered the number of drugs used to be a better outcome than use/non-use, since some patients used more than one, and reductions or increases would be assessed in this approach.

Pulse, along with systolic and diastolic blood pressure, was used to see how deprescribing affected these measures. Deprescribing was defined as using more antihypertensives at baseline than at month four. We did not continuously track changes in drug use; instead, we relied on drug use at three time points: baseline, month four, and month nine. Most changes appeared between baseline and month four. This is where the active intervention occurred, and hence is the period of major interest.

As the use of antihypertensive drugs is a count variable, a Poisson regression was appropriate [157]. For the continuous outcomes pulse, systolic, and diastolic blood pressure we used a linear regression [153]. The change over time in antihypertensive use was different in the intervention and control group, so the analyses investigating the association of high vs low/normal blood pressure and cognitive status were stratified on group allocation. Deprescribing of antihypertensives was rare in the

control group, so we did not investigate the effect of deprescribing on blood pressure and pulse in the control group.

4. Ethics and approvals

All studies had the approval of the regional ethics committees before initiation of the studies. Paper 1 also had approval from the Norwegian Data Protection Authority and the Directorate for Health and Social Affairs. The COSMOS study was registered in clinicaltrials.gov. All the registrations, approval numbers and references are listed in the papers.

The inclusion period for the patients in my papers stretched from 2004 to 2015. During that time, the Norwegian law regarding requirement of informed consent has changed. This is reflected in the different approaches to obtain consent: For the 2004 cohort in Paper 1, a written informed consent was not required, but the patients were informed that they could withdraw from the study. For the 2007 and 2011 cohort and for the COSMOS study, a written informed consent was required for participation.

Written informed consent is a prerequisite when doing research involving humans [158]. A person must be informed about "aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal." [158]. Patients with moderate to severe stages of dementia are often unable to grasp abstract aspects and understand consequences of their choices [159]. For this reason people with dementia, are generally excluded from trials testing effectiveness of drugs [98].

The Declaration of Helsinki clearly states that underrepresented groups should gain access to taking part in research [158]. It also states that one should provide special care when doing research on vulnerable groups, and informed consent is the rule. However, for patients lacking the ability to understand an informed consent, a legal guardian can accept participation on behalf of the patient. This requires a special focus on "do no harm" and that the research could not be done on patients unable to consent.

The first paper collected data about the patients. Still, the patients were not involved in data collection and they were not interviewed. This ensured minimal burden on the patient, while they were still contributing to research concerning their daily life.

The COSMOS study used five well-known and tested interventions in nursing home patients; the novelty was to test these together to try to improve the quality of life for the patient. If effective, this would have an immediate benefit for the patient. At the same time, the interventions posed a minimal risk, as they have already been tested individually [151].

To collect consent in the COSMOS study, we approached all units in the nursing homes with information about the study. The information was distributed to the staff and patients. In addition, we sent a letter with information about the study to the next of kin of the nursing home patients. The patients' capacity to give informed consent was judged by the researchers in a direct talk with the patient. The talk consisted of oral and written information about the study and an MMSE test. If the patient was deemed capable of signing the consent form, a written consent was obtained if the patient wished to join the study. All the next of kin were called and informed about the study regardless of the patient's cognitive status. If the patient was not capable of signing an informed consent, the next of kin was asked to sign a presumed consent on behalf of the patient. The patient, next of kin, and nursing home staff were informed that the patient could withdraw from the study at any time without giving a reason.

By ensuring that the trials had the proper approvals and were registered in the online database before initiations, we also ensured that the trials had a clear plan of recruitment, dissemination of the study, a priori hypotheses, and a plan for reporting results, thus increasing the transparency of the trials [158].

5. Results

5.1 Paper 1

Gulla C, Selbaek G, Flo E, Kjome R, Kirkevold O, Husebo BS. Multi-psychotropic drug prescription and the association to neuropsychiatric symptoms in three Norwegian nursing home cohorts between 2004 and 2011. BMC Geriatr. 2016;16:115.

Main findings:

- Included 4739 patients from 129 nursing homes
- The patients used an average of 6.6 drugs and 80% had dementia
- 73% used psychotropics; 32% one, 24% two, and 17% used three or more. Range: 0–7
- 39% used antidepressants, 30 % used sedatives, 24% used anxiolytics, 20% used antipsychotics, and 14% used anti-dementia drugs
- A high degree of NPS was most strongly associated with use of multiple psychotropics (OR 1.02, 95 % CI 1.02–1.03). Mean NPI-NH for patients not using psychotropics were13.5 (SD 16.3), while for patients using ≥3 psychotropics it was 25.5 (SD 21.8)
- This association was especially strong for depressive symptoms (OR 1.10, 95% CI: 1.09–1.12), where mean NPI-NH was 1.8 (SD 3.5) for patients using none, and 3.9 (5.2) for patients using ≥3
- The women, the younger patients, the patients more independent in daily living, and those with a recorded diagnosis of dementia were more likely to receive more psychotropics

5.2 Paper 2

Gulla C, Flo E, Kjome R, Husebo BS. Implementation of collegial mentoring and systematic clinical evaluation in nursing home patients in a cluster randomized effectiveness-implementation clinical hybrid trial: Introducing a novel strategy for multidisciplinary medication review. Submitted 2017.

Main findings:

- Included 297 intervention group patients in 36 units
- The patients used on average 7.6 (SD 3.8, range: 0–19) drugs and had 4.4 (SD 3.3) diagnoses
- The most prescribed drug groups were laxatives used by 172 (58%) patients, antithrombotics 155 (52%), and paracetamol 136 (46%)
- All units sent the required two participants to the COSMOS education program. Of these 61% were registered nurses, 12% licensed practical nurses, and 27% of unknown education. Seven (33%) of the physicians participated
- 13 (62%) of the physicians had a specialty, 12 of which were in family medicine, one in internal medicine
- 55% of the units had the majority of the staff hired for part-time positions
- The physicians attended for averagely 22 patients (range: 8–28) of the patients in the study
- 33 (11%) patients died during the study
- All the units endorsed the medication review intervention, and 92% of the patients received a medication review during the first four months of the study
- Facilitators towards implementation were the enthusiasm the intervention created and improved communication between all the involved parties
- Barriers were lack of time, difficulties in involving the staff and physicians, and ethical dilemmas concerning prescribing

5.3 Paper 3

Gulla C, Flo E, Kjome R, Husebo BS. Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure. J Geriatr Cardiol. Accepted.

Main findings:

- Included 164 intervention patients, and 131 control patients, using 9.2 drugs on average
- 43% of the patients had a diagnosis of hypertension, 79% had a cardiovascular diagnosis, hence 21% had no cardiovascular diagnosis
- The other frequent cardiovascular diagnoses were: atrial fibrillation (23%), heart failure (17%), and stroke (16%)
- Mean blood pressure at baseline was 128/71 mmHg, 9% had a systolic pressure ≥160 mmHg and 5% a systolic pressure <100 mmHg
- The average number of antihypertensives were 1.6
- Between baseline and month four there were 19 (12%) mortalities in the intervention group, and 17 (13%) in the control group. Between month four and nine 17 (12%) died in the intervention group, and 12 (11%) in the control group
- Between baseline and month four, seven (5%) were hospitalized in the intervention group, and 14 (13%) in the control group. Between month four and nine, seven (6%) were hospitalized in the intervention group, and 12 (13%) in the control group. The hospitalization rates were higher for the control group at both time points (p=0.031 and p=0.041)
- Significantly more drugs were reduced in the intervention group. A reduction was seen among 32% of the intervention patients and 10% in the control group (Incidence Rate Ratio: 0.8, 95% confidence interval: 0.7-0.9)
- For patients with a reduction in an antihypertensives, the systolic pressure rose on average 14 mmHg from baseline to month four, but had decreased to baseline levels by month nine

6. Discussion

6.1 General considerations

In this thesis, I wanted to examine how to optimize prescribing for two major contributors to polypharmacy: cardiovascular drugs and psychotropic drugs. The focus has been on long-term care patients over 65 years of age. To improve prescribing, one needs to know the nursing home setting and the patients; these factors are investigated in papers 1 and 2. Papers 2 and 3 describes the development of the method for systematic medication review and reports on the effects. The following discussion will highlight important aspects when doing research on people with dementia and when performing such research in nursing homes.

When discussing the individual papers, I will focus on how the strengths and limitations are related to internal and external validity. Internal validity is the extent to which the results are true for the setting in which and the population for whom the study was conducted. The external validity refers to how results can be generalized the results to other settings and populations [160].

6.2 Considerations on study types

Paper 1 examines the relationship between multi-psychotropic drug use and patient characteristics. Paper 1 uses a cross-sectional sample, even though the cohorts were from different years. Another way these data could have been analysed is to look for time-trends in the prescribing and correlations, and then describing development over time. Time trends in use have been mapped in Norwegian samples [78], and our data showed consistent associations over time. Cross-sectional investigations of associations have also been performed before [128, 161-163]. All these studies demonstrate a high correlation between NPS and psychotropic drug use; some also report on multi-use. However, none of these studies has focused on whether there is an association between more severe NPS and the use of more psychotropics. This could only be done in a large cross-sectional study.

Papers 2 and 3 are both based on the COSMOS study. A complex design was required for the COSMOS study because of the involvement of many different professions and interventions [15]. The design entailing five interventions was chosen due to the lack of proven effect on quality of life from previous studies that investigate single item interventions [9]. The project leader (BS) had also experienced in earlier studies [77] that the staff asked for a broader approach incorporating more aspects of the patient's real life in the nursing home. The goal was that interventions would reinforce each other. Complex interventions are common when investigating nursing home patients, and 53% of the studies involved in the reviews listed in Table 1.5.3 are complex.

The COSMOS study was also a hybrid study, which means that we could assess the implementation and effectiveness of the intervention in the same study [164]. This design is ideal for complex interventions. To reduce the barriers against implementation, we needed a study we could adapt to the local setting.

The COMSOS study was a single blinded study. In our case, this means that the patients were not informed which group they belonged to. Only a minority of the patients had cognitive capacity to understand that they were part of the study. None of the primary outcomes in Paper 2 or 3 include direct answers from the patients; hence, the patients knowledge about group allocation would not affect the results. We did not blind the participating staff or researchers. The reasoning behind this was that the assessment could only be done by staff with knowledge about the patient, and an important goal in the COSMOS study was to involve all staff in the units. Hence, staff performing the intervention could not be blinded to group allocation.

The intervention consisted of training, education, medication reviews, and close follow-up. This was performed by the research team. This team was also responsible for data collection, and was therefore aware of group allocation.

6.3 Discussion of the methods

6.3.1 Paper 1

Internal validity

By including three cohorts of Norwegian nursing home patients over a period of eight years, and with over 4 000 patients, we could ensure a high internal validity by a good representation of Norwegian nursing home patients. The patients in all three cohorts were assessed following the same procedure, which increases the strength of the findings. A limitation is the difference in obtaining consent over the years; this resulted in a lower recruitment rate in the two latter cohorts. We have no comparison between excluded and included patients, and cannot say whether this affected the results.

We compared the cohorts, and we found that the 2004 cohort consisted of slightly younger patients, who used fewer drugs. This is in line with what we would expect, since the average age of nursing home patients has increased and the use of drugs is rising [40, 78]. The 2004 cohort was placed between the 2007 and 2011 cohort regarding level of NPS, dependency, and cognitive function. Hence, the difference in recruitment does not seem to have affected the cohorts to any noteworthy extent.

Assessment of people with dementia

When assessing people with dementia, proxy rating of symptoms is essential because the patients are often unable to report these symptoms themselves [62].

An important aspect to consider when choosing which instruments to use is the quality of the instruments. The Consensus-based Standards for the selection of health status Measurement INstruments (COSMIN) checklist was developed to assure the quality of health status instruments [165]. An expert panel went through a Delphi process where they first decided on the taxonomy for measurement properties, and found three overarching domains: reliability, validity, and responsiveness. The panel reached the following definitions [165]:

Reliability: The degree to which the measurement is free from measurement error.

Validity: The degree to which an instrument measures the construct(s) it supposed to measure.
Responsiveness: The ability of an instrument to detect change over time in the construct to be measured.

The expert panel then constructed a checklist for evaluation of studies evaluating instruments [166]. All the instruments used in this paper have a high quality according to the COSMIN criteria. The instruments are widely used in both clinical practice and research, and are readily available online in Norwegian. This makes the results easier to compare with other cohorts and between countries.

External validity

The sample constitutes an unselected group of nursing home patients from all types of units and from the greater part of Norway. It is reasonable to assume that these results are representative for most nursing homes in Norway and comparable countries.

In the two latter cohorts, the main cause of exclusion was lack of obtained consent, most often because the next of kin failed to provide consent on behalf of the patients. To consider consent is especially important when doing research on people with dementia, as this group has routinely been excluded from studies due to lack of ability to give informed consent [159]. The exclusion of people with dementia because of difficulties with informed consent would leave us with a small, highly selected, and non-representative sample of patients left when studying nursing home patients. These patients have a lower rate of NPS than patients with dementia [167]. Such exclusion would reduce the generalizability to a typical nursing home unit. Consent should therefore be given as presumed consent by a relative or legal guardian [158]. Given that the rates of dementia in all three cohorts are comparable, we do not have reason to believe that patients with dementia were excluded to a greater degree in the two latter cohorts.

6.3.2 Paper 2

Internal validity

The COSMOS study was broad and complex. The design made it possible to adjust the intervention to the needs of the participants [15]. This introduces more variability and may thereby decrease the internal validity of the results, because the participants received somewhat different interventions. However, the method of recruitment and data collection was the same across units, thus increasing the internal validity. The medication reviews followed the same structure in all units, and we strived to keep the given advice and degree of participation consistent. We experienced that the physicians and nurses did not have the same needs in the different units, and we saw it as necessary to adjust our involvement. Figure 6.3.1 is an outline of the different processes in the COMSOS study from Paper 2.

In hindsight, it would have been favourable to use a more systematic approach to assess the implementation process to increase the internal validity of the implementation results. Nilsen (2015) [168] described five different categories of theories or frameworks that can be used in implementation science. For evaluation of implementation, he recommends evaluation frameworks like RE-AIM [169], Proctor's framework [170], or PRECEED-PROCEED [171]. These frameworks suggest areas that should be evaluated in implementation studies.

A recent review aimed at investigating which elements according to the RE-AIM framework were important for implementation of psychosocial interventions in nursing homes [172]. By looking at what the review found and comparing that to what we report, we can consider to which degree we report on implementation compared to other studies. The review found that 22% of studies reported *reach* (the proportion of individuals partaking in the intervention), with a variation between 34-97%. For our study, we met the goal of two staff participating in the intervention per unit, giving 100% reach, for the physicians the reach was 33%.

The review divides *effectiveness* into knowledge about the intervention and attitudes and skills of the staff. The review found that implementation strategies that included

training and follow-up, were most successful in improving knowledge, but had minimal effect on attitudes or skills. They recommend educational sessions for the staff with the addition of follow-up sessions or support of staff. These elements were present in the implementation of the COSMOS study. We did not systematically assess the staffs' knowledge about the intervention, and we cannot say whether the intervention affected this.

Adoption was defined as the proportion of caregivers adopting the intervention, and was often neglected by the studies in the review. We have no numbers on percentage of the staff performing training and medication reviews, but we do know that all physicians in our study adopted the intervention. All units logged the intervention, and we have a log of the intervention for 92% of the patients.

Regarding *implementation*, the RE-AIM review identified factors like percentage of perfect delivery, adaptions to the study, costs, and factors affecting implementation. On these matters, we reported that 92% of the patients received the medication review, and six units received an additional medication review because they felt a need for more support to ensure implementation. We also report on barriers against and promoters of the implementation.

The final aspect of the RE-AIM is *maintenance*. The review points out that there was little maintenance of the interventions after six and nine months in the included studies. We report data after four months on whether the intervention occurred in the first four months. In Paper 3, we also demonstrate how the effects are greatest in the first four months. As a note to this, I would like to mention that following the month-nine data collection, all the participating units were given the initial educational programme, where both intervention and control units were invited. Two of the municipalities have also invited us to three additional days of courses for the initial units and additional units. In one of these municipalities, the council has decided that all nursing homes should follow the COSMOS approach, and the other municipality is looking into doing the same.

The feedback on promoters and barriers was given primarily during the midway seminar. Other sources were feedback during the medication reviews and from open-ended questions in the patient logs. The feedback from the midway seminar was given in the same manner from all units. We used a traffic light approach, which is widely used in evaluation of teachers and lessons for the units to evaluate the intervention. This is not a standard approach for collecting barriers and promoters. However this was a part of a process evaluation of the implementation [15] and served as a thermometer for challenges and promoters relevant to the trial. It also lead to sharing of solutions across units.

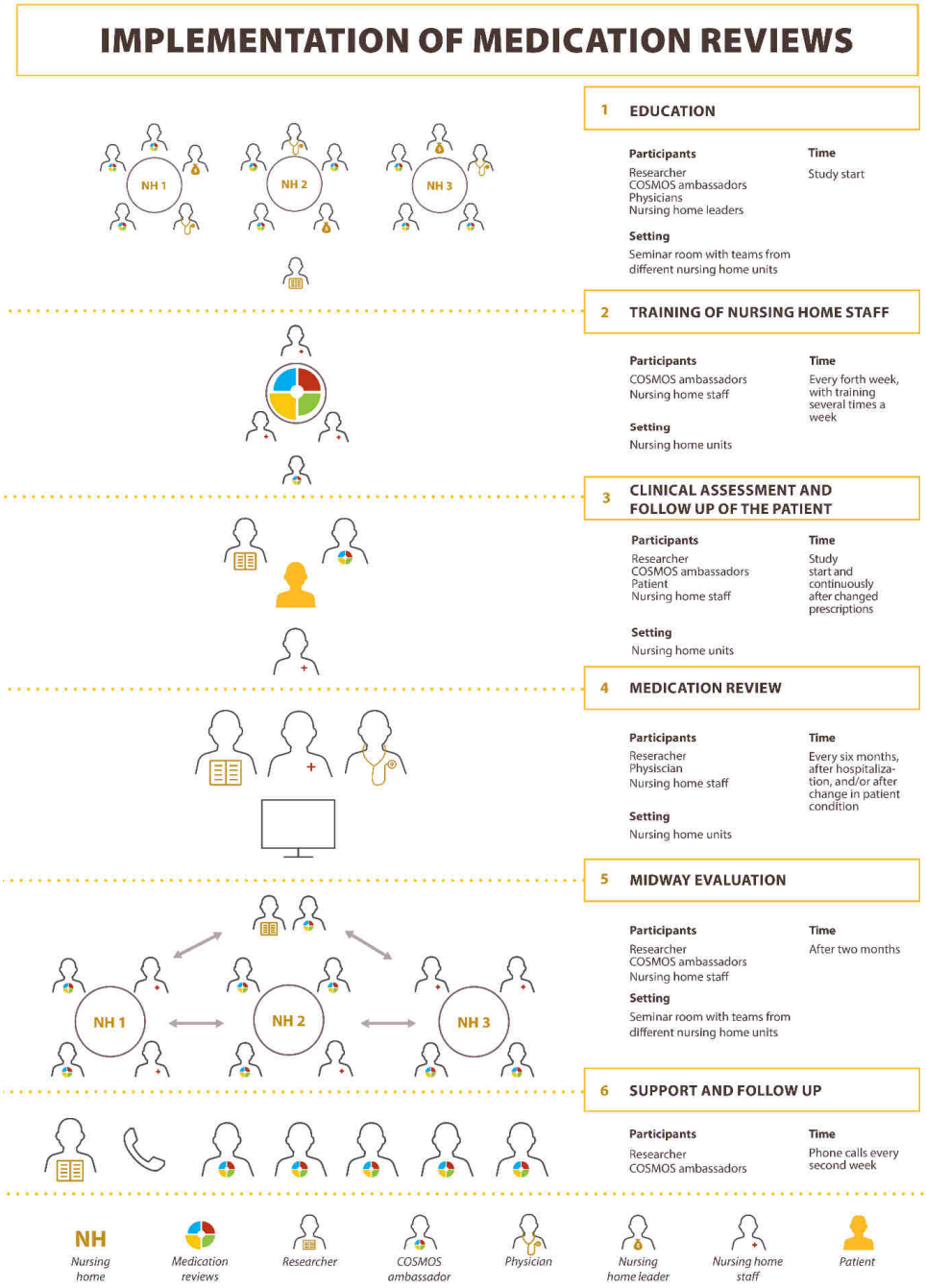

Figure 6.3.1 **The implementation process in the COSMOS study from Paper 2**

External validity

The effects we observe in Paper 3 cannot be attributed to the medication review alone. The changes may be influenced by the other elements in the study. All the patients and relatives, for instance, were invited to have conversations about advance care planning. Through these conversations, it is likely that the patients, relatives, and staff had a better understanding of the patient's prognosis and health [173]. A definite goal was to increase the quality of life for the patient and offer individualized activities for the patients. These factors were involved in the medication reviews and may have facilitated deprescribing of preventive drugs. However it is advocated to include patient and relatives in discussions about drug use in the patient-centred care approach [127]. This increases the external validity by using an already well-known method.

We wanted to measure the degree to which the intervention was implemented and what barriers and promoters were involved. The individual adjustments to each nursing home reflects how one would have to implement a new procedure in "the real world" and increase the external validity. By also assessing adaption of the intervention to each nursing home, we increased the transferability of the results to other nursing homes by learning from our experiences.

6.3.3 Paper 3

Internal validity

As Paper 2 describes many of the methodological issues of the medication review intervention in the COSMOS-study, many of the factors related to validity are discussed above. However, some issues have not yet been addressed. Because we randomized units rather than physicians, some of the participating physicians worked in both intervention and control units. As discussed in the paper, this may mean that the interventions of the study bled over to the control groups. If this is the case, the differences between control and intervention groups may be underestimated.

Lack of blinding may lead the nurses to overestimate the effects when scoring the patients. The outcomes in this paper use information on prescriptions from the

electronic patient records and blood pressure measured by nurses. It might be a reasonable to believe that these outcomes are less affected by blinding than more subjective measures of improvement, pain, and agitation.

We used the same assessment scales and procedures on all patients before the medication reviews. This ensured that decisions were based on equal grounds. The blood pressure, pulse, weight, and height were measured according to local routines. We observed a huge variability in these routines. The blood pressures were measured with automatic devices, however not repeated three times as recommended [90]. The pressures were measured at all times of the day and with the patient either lying or sitting. This increases the variability of the measures even further. However, the variability should be similar in both groups, and less variability would most likely have increased the strength of our findings. It is also important to point out that these measures are the ones that the physicians rely on when they evaluate the treatment, leading to the discussion of external validity.

External validity

In this study, we chose the patients based on the drugs they were prescribed, not diagnoses. The drugs all had hypertension as one of their main indications. However, there are also many other indications for these drugs, like heart failure or atrial fibrillation. The method of selecting patients by drug use has also been used by other studies to identify patients with hypertension [174], and the drugs were coded according to an international standard to increase transferability [148]. The fact that 21% of the patients did not have any cardiovascular diagnoses in their medical records also underpins the method of using prescriptions, rather than diagnoses, to select patients. This is further highlighted by the finding from Paper 1, where there was only a small correlation between having a dementia diagnosis on record, and having dementia according to CDR [167].

The medication review method used in COSMOS was chosen by evaluating the studies included in the reviews listed in Table 1.5.3 (we used the 2013 edition of Alldred et al. [175]). NPS was assessed in nine of the 39 studies involved in the

reviews, and pain in one. Since drugs treating NPS and pain are among the most frequently prescribed [5], we wanted to include validated instruments for these conditions to be able to evaluate whether the prescribing was appropriate.

To further evaluate the prescribing, it is necessary to know the patient's cognitive status and level of functioning. High quality of life is a good goal, and a measure of this goal was a good starting point for a discussion on what we could do to improve the life of this patient. We used a set of validated tools for people with dementia to address these symptoms and areas (see section 3.1.1 for a description of the instruments), and we used the results actively in the medication review. To our knowledge, this is the first study to use this wide and systematic assessment approach in medication reviews.

The nursing home physician is the person responsible for prescribing, and 28% of the studies identified by the reviews directly involve the nursing home physician in the intervention (these studies are listed in Table 6.2.1) [176-187]. The studies are primarily randomized controlled trials involving from 63 to almost 2000 patients in nursing homes. Three of the studies also involve the physician in multidisciplinary medication reviews. All of these were over 10 years old at the initiation of COSMOS. The fact that we included the physician made the intervention closer to day-to-day practice and increased external validity.

Deprescribing is difficult, partly due to professional loneliness and academic uncertainty [188]. The COSMOS study introduced a colleague (collegial mentoring) to lessen the burden of deprescribing. Visiting colleagues is an accredited part of the specialization program for general practitioners in Norway, so the physicians have an incentive to give collegial mentoring already.

Table 6.2.1 **Characteristics of studies included in the systematic reviews with direct involvement of the physician.**

Author (year)	Country, number of participants	Design	Aim	Intervention	Conclusion
Connolly (2015)	NZ N=1998	cRCT	Reduce avoidable hospitalizations	Education to staff, MDMR	No effect on avoidable hospitalizations or mortality
Frankenthal (2014)	Israel N=359	RCT	Assess effect of using START/STOPP on clinical and economic outcomes	pMR, case-conferencing	Intervention group had reduced number of drugs, falls, and cost. Hospitalization, dependency and quality of life were not affected
Olsson (2010)	Sweden N=302	CT	Examine if patient focused drug surveillance improved quality of drug treatment	Education, audit	Intervention group had reduced number of drugs, and increased monitoring and evaluation of drugs. No difference in mortality.
Colon-Emeric (2007)	US N=606	cRCT	Improve fracture prevention	Education to staff, educational material, audit, case-conferencing	No effect on fracture prevention. Low attendance in intervention activities, but participation in education and case-conferences was associated with improved fracture prevention.
Crotty (2004c)	Australia N=715	RCT	Improve evidence based clinical practice for fall reduction and stroke prevention	Education to staff, pMR, case-conferencing	No difference in fall rates, psychotropic drug use, or stroke prevention.
Crotty (2004a)	Australia N=154	cRCT	Improve appropriateness of prescribing and patient behavior	Education to staff, MDMR, case-conferencing	Appropriateness of prescribing improved, while patient behavior was unchanged.

Table 6.2.1 **Continued**

Author (year)	Country, number of participants	Design	Aim	Intervention	Conclusion
Crotty (2004b)	Australia N=110	RCT	Improve drug management and health outcomes after transfer from hospital	Education to staff pMR, case-conferencing, transfer coordinator	No change in appropriateness of drugs in intervention, and a worsening in controls, less pain and hospitalizations. No difference in adverse drug events, falls, mobility, behavior, or confusion. Low attendance at case-conferences.
King (2001)	Canada N=245	CT	Improve outcomes for patients and carers	MDMR, case-conferencing	No effect on drug use, cost, or mortality. Changes were beneficial for patient and carers.
Claesson (1998), Schmidt (1998)	Sweden N=1854	RCT	Reduce inappropriate drug use, and reduce psychotropics	MDMR, case-conferencing	Drug use increased. Psychotropic use was unchanged in intervention patients and increased in controls. Decrease in antipsychotics, benzodiazepine hypnotics, and antidepressants.
Cavalieri (1993)	US N=63	RCT	Improve health outcomes	Geriatric outreach team	More diagnoses and use of medical services. No difference in mortality, hospitalizations, or drugs.
Avorn (1992)	US N=823	CT	Reducing psychoactive drugs, and clinical outcomes from reductions	Education of staff and physicians	Reduction in inappropriate psychotropic prescribing. Decrease in antipsychotics, long-acting benzodiazepine, and antihistamine hypnotics. Less decline in cognition, more depression if antipsychotics were reduced. Less anxiety and more cognitive decline if benzodiazepine or antihistamine hypnotics were reduced.

cRCT: cluster randomized controlled trial, CT: controlled trial, MDMR: multidisciplinary medication review, NA: not applicable, NPS: neuropsychiatric symptoms, NZ: New Zealand, pMR: pharmacist medication review, RCT: randomized controlled trial

Prior to the start of the study, the Norwegian Patient Safety Campaign had held an extensive campaign advocating medication reviews for the nursing home patients [189]. Their method included the use of the START/STOPP criteria, a designated checklist of symptoms, suggested lab tests, and a pharmacist visiting the nursing home. It was therefore natural to build our method on their approach to increase external validity.

The pharmacist is used in numerous studies to improve or evaluate prescribing (Table 1.5.3). These studies often show beneficial effects. We also invited the nursing homes to include their pharmacist in the medication review. Sadly, none of our nursing homes had one available for these sessions.

The data on drug use were collected at three time points; baseline, month four, and month nine. We did not track changes between the data collections. The medication reviews were performed in the first two months of the study, giving the physician and patient at least two months to evaluate changes after the medication review. During this period, the patient could be put back on the drug if the change was not beneficial. We therefore believe that the prescriptions we see at month four are the results of true changes, rather than unsuccessful pauses. Clinicians testing this intervention might therefore experience a lower rate of success – because we did not record the "unsuccessful withdrawals".

6.4 Discussion of the results

All the articles show an extensive use of drugs in nursing home patients. The first paper found that each average patient uses 6.6 regular drugs; the intervention patients in COSMOS used 7.6, and the patients using antihypertensives used on average 9.2 drugs each. In Paper 1, the patients in the 2011 cohort used more drugs than in the 2004 and 2009 cohorts, and comparing this with the COSMOS results from 2015–2016, indicates that drug use is on the rise. In light of the fact that that polypharmacy is an individual risk factor for adverse drug events, inappropriate drug use, and falls [3], this development cannot be allowed to continue.

Psychotropic drugs are an important factor in polypharmacy, and in Paper 1 we found 73% of the patients use psychotropics. Some patients even use up to seven different drugs from this group. Such drugs are important in the treatment of psychosis, agitation, depression, and insomnia [69]. However, when we look at the evidence for treatment displayed in Table 1.3.1, the effects are minor. A shortcoming with a cross-sectional study is that we do not know why and for how long these patients had had drugs prescribed for them, and we do not know whether there had been any previous attempts to deprescribe. A patient expressing severe NPS might have had an improvement since the start of the drug, in which using the drug would be appropriate. A patient could also have recently started taking a drug, and the effect might not have set in yet. On the other hand, patients expressing a low degree of NPS may reflect a well-regulated drug regime, or excessive treatment. This raises the famous issue of the chicken and the egg: is it the NPS that leads to excessive psychotropic prescribing, or is it the excessive psychotropic prescribing that leads to NPS.

To reduce the use of psychotropics, we need to address the NPS. These symptoms have multifactorial aetiology [59], which might explain why drugs have so little effect in this group of patients. The NPS is both distressing for the patient and the caregiver [49], and this might create a call for action, often answered by the prescribing of psychotropic drugs [188]. We do not want the patient to suffer, so we would rather try a drug than to leave her in distress [188]. This might explain the extended use in the patients expressing the most NPS.

The first step towards management of NPS is a proper assessment of the patient [59]. Assessment should include investigating whether the patient is in pain, has an acute medical condition, a sensory deficit, or is overstimulated or understimulated. As discussed above, it is important to use validated tools when assessing NPS in people with dementia. In the studies included in the reviews mentioned in Table 1.5.3, NPS is systematically assessed in nine (23%) of the studies and four (10%) have a clinical assessment that might include a systematic assessment. However, information on whether the information was used in the intervention is lacking. Cognition was

assessed in 11 (28%) of the studies, and pain in one (3%). In Paper 2, we found that 94–97% had dementia, 67% neuropsychiatric symptoms and 52% pain. This highlights the necessity of including these assessments when performing a medication review both to be able to prescribe correctly, but also to be able to monitor significant changes.

Antihypertensive drugs were used by 50% of the COSMOS patients. High blood pressure, defined as systolic pressure ≥140 mmHg was present in 22% of the patients. If cut-off is set to ≥160 mmHg, high blood pressure was present in 9% . Tachycardia (>100 beats per minute) were present in 7%. These numbers suggest a substantial potential for deprescribing.

If we compare the MMSE scores of the intervention group in Paper 3 with those of unselected intervention patients in Paper 2, we see that the distribution is strikingly similar, indicating that patients with dementia receive as much antihypertensives as patients without dementia. A British epidemiological study of nearly 80 000 individuals aimed to investigate the outcomes of treating hypertension in people over 80 years [174]. They excluded patients with comorbidity to investigate the "pure" effect of antihypertensive treatment. They found a U-shaped association between mortality and systolic pressure, the lowest mortality was between 135–154 mmHg. This association remained the same when adjusting or stratifying for pulse-pressure, and a range of diseases. It seems that even for the healthiest of the old, a low blood pressure is dangerous and the ideal blood pressure is higher than for the young [90]. This information should aid deprescribing of antihypertensives in some patients.

Especially regarding psychotropic drugs, such as antipsychotics, there is increasing evidence that drugs can be discontinued without harmful effects to the patient [190]. However, there is no single, simple, one-solution-fits-all way of doing this [126], and the physician is crucial in this process. At the same time, deprescribing cannot be done in a safe and individualized manner without the involvement of the nursing staff. They must observe and assess the status of the patient before and after deprescribing, and in some cases offer non-pharmacological treatment to avoid

deterioration of the patient. Thus, involving both the physician and staff in the medication review improves both the clinical effectiveness of the intervention and increases patient safety.

There are many barriers to optimizing prescribing [188, 191]. An interesting result from COSMOS is that factors described by some units as barriers are described by other units as factors for success. This is also described by Boersma et al. [172]. This review identified important factors influencing the implementation of psychosocial interventions. The factors identified by most studies were time, support from managers, influence of quality of care enthusiastic and experienced team, and the conditions. Hence, knowledge about these factors, and cooperating across units, can increase success.

6.5 What does the COSMOS approach add?

The discussion above has focused on the individual studies and smaller aspects of the COSMOS study. There is no question that there are already multiple studies on medication reviews and methods to improve prescribing in nursing homes (Table 1.5.3). To invent a new intervention or test a new method might seem superfluous in regard to the variety already tested. However, we felt that there were some aspects not thoroughly enough investigated or considered.

The variety of symptoms

The patients experience a variety of symptoms [77, 167], and dementia renders the patients unable to explain or express these symptoms. Hence, we needed to systematically address these symptoms for them.

Involving the physicians

It is striking that the physician responsible for the medical treatment of the patients is often not directly involved in the studies (Table 6.2.1). In the end,

the physicians are the ones prescribing the drugs and the ones in charge of monitoring the patients' health. To ensure a lasting change, the physicians need to be involved in the process.

Identify barriers and promoters

There is a widespread understanding that polypharmacy is harmful and we should all work towards optimal prescribing [9]. Still, the use of drug prescription is increasing [4, 78]. To improve prescribing we needed to address some of the barriers to deprescribing. Some of these are known from studies [188], and some from our own experiences. One particular characteristic of working as a nursing home physician in Norway is that one most often works as the only physician in the institution. This is contrary to physicians in hospitals experiencing daily contact with colleagues. Having support from colleagues can make it easier to make difficult decisions.

There are also numerous barriers and promoters relevant to changing a practice in an institution. We examined these as we conducted the study, and are therefore able to tailor the intervention to each nursing home, to increase the possibility of implementing the intervention [164].

7. Conclusion

The overarching goal of this thesis was to explore how to optimize prescribing for two of the major drug groups contributing to polypharmacy, and describe the implementation process of the medication reviews in the COSMOS study.

We found an extensive use of psychotropic drugs, and the use was strongly connected to degree of NPS. Antihypertensive drug use was also high, regardless of cognitive status. Patients with advanced dementia also had fewer drugs prescribed drugs deprescribed.

Through education and collegial mentoring, all patients in the intervention group received medication reviews. Barriers such as of time were reduced and ethical dilemmas addressed. The clinical medication reviews reduced the use of preventive antihypertensive drugs, without increasing hospitalization or mortality. A decrease in these drugs led to an initial increase in blood pressure, however the increase was not sustained over time. This demonstrates that the medication review is an ongoing process that requires continuous hands-on contact with the patients, their demands, wishes and diseases.

Seeing these results holistically should increase the awareness of drug use in nursing home patients. There seems to be an extensive use of drugs, and a great potential for deprescribing. To successfully deprescribe, some elements are essential. We need to take into account that most patients have dementia, will experience NPS, and that pain is very common. Therefore, to evaluate which drugs should receive precedence in treatment, these symptoms must be properly assessed as a part of the medication reviews.

By consolidating education, collegial mentoring, and multidisciplinary medication reviews, we intended to increase the knowledge of all actors involved in prescribing. We discussed the challenging aspects of prescribing together and this facilitated discussion on difficult ethical dilemmas. The focus on tracking the effect of drugs, and trying to pause drugs, led to a reduction in drug use.

8. Implications for further research

This thesis investigates a small part of prescribing for the nursing home patients. This small part has uncovered an extensive use of psychotropics and a substantial nuber of neuropsychiatric symptoms. We have also found a method that ensured the patients received medication reviews, and decreased the use of preventive drugs.

This researchs builds on and extends the research at Centre for Elderly and Nursing Home Medicine, Department of Global Public Health and Primary Care, University of Bergen. This centre aims to conduct research to improve the life of elderly in the municipalities, implement research, educate health care professions and the community, and collaborate nationally and internationally.

The next step after this thesis is to investigate how to implement the medication reivews in more nursing homes by expanding the project and disseminate it to new municipalaties by education collaboration. The research has already been spread and implemented in Norway beyond the included nursing homes. The COSMOS education program has been optimized and delivered to ten new municipalities. This shows how Norwegian nursing homes are focusing on improving care.

Another question left unaswered is how overall prescribing was affected and which drugs were changed the most. Even more importantly – we do not know how the patients' quality of life or symptoms changed throughout the study period. Being a complex study, with multiple interventions it is reasonable to believe that it was more than the medication reivews that caused changes for the patiets, so these questions must be investigated as a whole.

The intervention took considerable time to implement and investigate and we do not know whether it was a cost-effective intervention. One of the more interesting themes emerging when visiting different units and analysing the data was the variability between units and physichians in prescribing and change. A greater effort should be made to investigate these differences.

All these papers investigated nursing home patients, however we see an increase in home-dwelling elderly. A trial extending this research into the home dwelling has partly sprung out of the COSMOS study and will investigate if the intervention can translate into home care.

9. Implication for the clinician

The COSMOS study was a complex study with many moving parts. It took considerable effort from the involved parties to attend and for the researchers to organize. To translate this into clinical practice, one probably needs a coordinator or resource person who can help the units with practical difficulties, finding soulutions and gathering the units for problem solving and sharing. This has been solved by some of the municipalities involved by reorganizing the tasks for people alredy connected to the nursing home management.

To assess all patients requires a great deal of resources and knowledge. However with basic training, most of the staff were able to perform the assessments. And in the other end, this increases the speed of the drug review itself, since we aldready had the knowledge to evaluate the drugs in question. A reduction in the number of drugs will also reduce time spent on preparation and administration of the medication.

The medication reviews led to improved communication between the physichian and nurses, and caused enthusiasm. The use of preventive drugs were also reduced. The collegial support lessened the burden of making diffucult decisions alone. In March 2017, a new regulation from the Norwegian government mandates that every physician working in a nursing home is required to have a speciality or be under specialization. Clinicians should use this opportunity to visit each other, discuss with peers, and focus on what's right for the patients – not what's right for one disease at the time. This is a part of the specializtion programme and a part of working in a demanding enviroment.

The studies could not have been accomplished without support from the people in the nursing home sector. This includes all personnel working with the patients, unit managers, nursing home managers, physicians, and key persons in the municipality. The involvement of the managers ensured that the personnel had the resources needed to carry out the study. The staff in the units did all the extra work concerning data collection and implementation. All this extra effort was not funded through the study or by the government. This is in contrast with the model for research funding in the

hospitals, where funding is received for doing research. It might be time to reconsider how research in the municipalities is dependent on the economic resources of the individual city.

Together we can do our best to lessen the burden and end polypharmacy for the frailest in our society.

I will now go back to where I started my story: the nursing homes. My next step will be to implement this into my everyday clinical practice, and hopefully be able to spread this knowledge to other nursing homes.

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10. Appendix

10.1 Ethical approval

Forskningsprosjekt

Forbedret mental helse hos pasienter boende på sykehjem. En klynge randomisert studie. (KOSMOS studien)

Vitenskapelig tittel:

Improving mental health in residents of nursing homes: A cluster randomized clinical trial of efficacy. (KOSMOS Study)

Prosjektbeskrivelse:
Sykehjemspasienter har komplekse helse utfordringer, funksjonshemninger, sosiale behov og overforbruk av medikamenter. KOSMOS (Kommunikasjon, Smertevurdering og – behandling, Medikamentgjennomgang, Aktiviteter og Sikkerhet) kombinerer mest effektive forskningsresultater for å øke personalets kompetanse, pasientens velvære, sikkerhet, og livskvalitet. Metoden inkluderer 2 måneder pilot studie, 4 måneder RCT, follow up etter 9 måneder. Effektmål (QUALID; EQ-5D; CMAI; NPI-NH; ADL; Cornell; MOBID-2; QUIS; antall medikamenter m.m.) innsamles i begynnelsen, måned 4 og 9. 480 pasienter (≥65 år) fra 60 sykehjem i Bergen, Stavanger, Oslo/Bærum og Sogn/Fjordane inkluderes. Alle sykehjem får tilbudt om kommunikasjon. Ved match paired randomisering vil institusjoner bli fordelt til kun kommunikasjon, eller kombinasjon av tiltakene smertevurdering og – behandling, medikamentgjennomgang og/eller aktiviteter. Statistiske analyser inkluderer Chi square, Mann-Whitney U, ANCOVA, og faktoranalyser.
(Prosjektleders prosjektbeskrivelse)

Ref. nr.: 2013/1765 Prosjektstart: 02.01.2014 Prosjektslutt: 31.12.2017

Behandlingsstatus: Under behandling
Prosjektleder: Bettina Husebo
Forskningsansvarlig(e): Universitetet i Bergen
Universitetet i Bergen
Initiativtaker: Bidragsforskning
Finansieringskilder: Norges Forskningsråd 222113

Forskningsdata: Mennesker
Utvalg: Pasienter/klienter, Personer med mangelfull samtykkekompetanse
Forskningsmetode:: Statistiske (kvantitative) analysemetoder
Antall forskningsdeltakere (Norge): 310

Utdanningsprosjekt/doktorgradsprosjekt: Studium: Medisin, Nivå: Ph.D

Behandlet i REK	
Dato	**REK**
13.02.2014	REK vest

10.2 Consent

UNIVERSITY OF BERGEN
Department of Global Public Health and Primary Care

Name
Name
Adress

Information about the research project "KOSMOS".

Dear relative/legal guardian.

You receive this letter because you are registered as next of kin/legal guardian of a patient in a Norwegian nursing home that is included in our research study.

Attached to this letter is an information letter about the project, a consent form, and a survey of your experiences with the nursing home. We will try to contact you by phone within a short period of time, to answer any questions.

Nursing home patients have complex issues related to clinical and social needs. An important goal for society is to safeguard patients' dignity and quality of life. This can only be done in nursing homes with high competence in treatment and care.

KOSMOS is a Norwegian abbreviation for communication, pain management, medication review, organization of activities and safety. The KOSMOS intervention is developed with a combination of the most important research-based results from international studies in mind. The goal is to increase patient cognitive wellness, safety and quality of life and to increase staff competence. It also aims to reduce pain, optimize prescribing and investigate the costs.

In February, researchers may try to collect data on all patients.

For any questions regarding this project: contact Christine Gulla christine.gulla@igs.uib.no, mobile +47 99727104 or Irene Aasmul irene.aasmul@igs.uib.no, mobile: +47 41164544.

Your contribution is very valuable.

Best regards

Project leader Bettina Husebø, PhD
Department of Global Public Health and Primary Care,
University of Bergen, NORWAY

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UNIVERSITY OF BERGEN
Department of Global Public Health and Primary Care

Requests to participate in the research project «KOSMOS» (Communication, Pain Assessment / pain management, Organization of activity, Medication Review and Security)

Dear GUARDIAN
You are next of kin/legal guardian of PATIENT,
a patient at NH in Bergen municipality.

We are contacting you because we want to conduct a project on the effect of increased focus on four key aspects of nursing home patients: communication, pain assessment / pain management, activities and reviewing medication. The KOSMOS project wants to look at the patient as a whole in order to increase quality of life.

KOSMOS includes a training program for the staff, as well as follow-up and implementation of the programs in patient's everyday life. Attached is an overview of what the study entails. Take the time you need to decide whether there is reason to assume that the patient would not wish to participate in the study. You are free to discuss our request with both the patient and other relatives.

What is included in the study?
In the study, the patient will be tested with well-known questionnaires to assess quality of life, dementia and pain. It is also possible that a patient will be drawn to wear an actigraph, a "clock" that measures sleep and activity rhythm. All patients receive a thorough clinical examination by responsible physician and project manager.

During the study, the wards in the participating nursing homes will be randomized to treatment groups or control groups. Patients in the treatment group will experience a systematic effort to increase nursing department expertise and focus on communication, pain assessment / pain management, activities and reviewing medication. This involves extensive training of nursing staff, and increased documentation of treatment and care that the patient receives. The nursing homes in the control group will be offered training and follow-up after the study is over.

Possible benefits
Our research group assume that such skills upgrading involves benefits for the patient, leading to improved quality of life and reduction of problems related to mental health. Well-known nursing- and treatment measures are now being systematically put together, with a tailored treatment towards each patient. It is emphasized that the study does not try out new treatment, but rather put together simple treatments that has previously shown to have a positive effect for nursing home patients. The study will be conducted in nine months with assessments at startup and after 4 and 9 months. Measurement of sleep rhythm occurs at startup and after 4 months. There is good reason to believe that the patient would like to have agreed to participate, he / she could have.

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The project is a particularly good collaboration between an international network affiliated with the University of Bergen, nursing staff, nursing homes and physicians from Norwegian nursing homes. It is expected to achieve a significant increase of expertise among staff related to communication, pain assessment / pain management, activities and medication.

Possible disadvantages
Such combinations of care and treatment interventions have not been tried out before. This could pose strain on nursing staff. The project tries to systematize knowledge that exists among professionals in Norwegian nursing homes, and one expects no side effects related directly to the patient's health.

What happens to the patient information?
The information recorded will only be used in purpose of the study. All information will be processed without names and identity numbers or other directly recognizable information. Each patient receives a code to ensure anonymity. Only authorized personnel associated with the project have access to this information, which are to be deleted when the project is completed in 2015.
It will not be possible to identify the patient when the study is published.

Voluntary participation
It is completely voluntary to participate in the study. You as the next of kin / legal guardian may at any time, without giving any reason, withdraw the consent to participate in the study. This will not affect the patient's further treatment. If you wish, on behalf of the patient, to participate in the study, please sign the consent statement on the next page.

Responsibility
The study conducted by the signer and Elisabeth Flo, psychologist, PhD, at the University of Bergen. When you sign the attached information form, you confirm that you have received this information letter and that there is no reason to assume that the patient would oppose to the investigation and individual pain treatment.

If you have questions or comments, please feel free to contact Irene Aasmul (fellow): +47 411 64 544 or Christine Gulla (fellow): +47 997 27 104.

Best regards.

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UNIVERSITY OF BERGEN
Department of Global Public Health and Primary Care

Consent for participation in the study

There is no evidence that the patient PATIENT residing in NURSING HOME in Bergen would not have participated in this study of the effect of an increased focus on four key aspects of nursing: communication, pain assessment / pain management, activities and medication review.

I am aware that the research team would like to register information about diseases and residence in a nursing home from the patient record. Information is treated confidentially and only information necessary for the study will be obtained.

I am aware that the patient's participation is voluntary and that the patient anytime can withdraw without further rationale, and that this will not affect the patient's future follow-up or treatment in the nursing home.

....
Signature (next of kin/legal guardian) Date

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10.3 Pocket card

MEDICATION REVIEW/MR

A multi-professional cooperation between nursing home staff, doctor, (pharmacist, if available), and the COSMOS-team to

- Optimize the patient's drug use
- Prevent interactions and side-effects
- Reduce unnecessary drugs
- Improve documentation and follow-up

Preparations before MR

- Blood tests, blood pressure, pulse, weight/BMI
- Clinical assessment with MMSE, Cornell, ADL, MOBID-2, CMAI, NPI-NH
- Interactions analysis
- START/STOPP criteria, anticholinergic drugs

WHEN AND HOW OFTEN?

- New MR after change in patient's condition, after hospital discharge, semiannually
- When the prescribing change, the patient has to be followed-up and the effect must be monitored
- Register changes and side-effects, there is no disgrace in reinstating a drug!

REMEMBER: Inform the treatment team, patient and relatives aboubt changes in the drugs

MEDICATION GROUP	ADVICE FOR CLINICAL EVALUATION
Antidepressants	No, mild, moderate, or severe depression? Cornell ≥ 7 indicates depression. Are prescribed antidepressants still indicated?
Anti-dementia drugs	Indicated in early stages of the disease. MMSE <12 – consider discontinuation. Consider memantine if agitated behavior.
Antipsychotics	Max 3 months. Mainly with delusions, hallucinations or delirium. Great risk of side-effects, use NPI-NH or CMAI.
Hypnotics	Short-time effect, risk of drowsiness and falls.
Anxiolytics	Short-time effect, risk of drowsiness, falls, and addiction.
Pain medication	MOBID-2 score ≥3 indicates pain – adequately treated/still indicated?
NSAIDs	Reduce heart- and kidney-function, increased risk of bleeding. Don't combine with SSRI, ASA, warfarin.
Blood pressure drugs	May give dizziness and depression. BT≤120/syst, or pulse<65/min – still indicated?
Anticoagulants	Consider discontinuation if a tendency to fall, still indicated?
Lipid-lowering drugs	>2 years life expectancy, may give muscle pain.
Laxatives	Lactulose may cause flatulence, macrogol: must be able to drink. With opiates: use contact laxatives.
Bisphosphonate, potassium, and Vit D	Is osteoporosis prophylaxis still indicated – is the patient still mobile?
Vitamins and minerals	Still indicated? Check: Hb, Cobalamin, homocysteine, folic acid, vit B-12
Anti-diabetic drugs	Check HbA1c; avoid low blood sugar – also at night.

READ MORE IN THE GUIDELINES!

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