Psychotropic drug use in older adults living in nursing homes

Associations with clinical symptoms and the effect of a structured drug review

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Table of Contents

Foreword and Acknowledgements

Once I finished medical school and I was ready to find a job as an intern, few positions were available in the little town I moved to in southern Norway. Therefore, I decided to accept whatever position was available at that time, and I started working as a nurse in a care home for older people. One of the tasks I was assigned to, was to prepare the daily medication each patient was prescribed by their physicians. The task itself was rather simple and mechanical: read the prescription list, find the right medication, and insert each pill in an organizer. As a freshly graduated medical student, I had no experience in the real clinical world; in school, I learned that each disease often corresponded to a specific pharmacological treatment a patient received. However, it still made me feel unease having to put 10 or 15 pills in a patient's organizer, each day. I had to quickly learn the commercial names of the most frequently prescribed medications, to be quick at my job, and I started to observe my patients, looking for signs and symptoms that corresponded to the treatment they received. Among the drugs I organized, tranquillizers, sedatives, and antidepressants were oddly very common in the medication lists. Many patients I had under my daily care had some sort of cognitive impairment, and once I got to know each of them, their personality, what they liked, what they were afraid of, and which resources they still had, I could not avoid thinking: "Do they actually need all these pills?".

A few years later, I started my career in psychiatry, but my curiosity and interest for the old patient care remained steady. During one of my first night shifts at the teaching hospital, I met an attending physician who worked in the psychogeriatric department. She introduced me to the complex and interesting subject of mental health in older patients. After a few years, I had the privilege of working in her department. I learned about dementia, psychiatric disease in the older people, and how to manage psychotropic drugs in these patients.

While working in old age psychiatry, I noticed that many patients referred to my clinic lived in a nursing home, and they already at the time of referral used several psychotropic drugs. This phenomenon was already described by several co-workers, and it corresponded well to my previous experience when I worked as a nurse in old-patient care. It made me curious to study and understand the possible causes of these high psychotropic prescription rates.

The beginning of my research career started with a simple discussion with my former clinical supervisor and colleague Astrid Haram. Thanks to her, I came in contact with my current supervisor, Sverre Bergh, an experienced colleague who introduced me to the world of research in old age psychiatry. My heartfelt thanks go to Sverre. He helped me developing this research project, he guided me from the very beginning, and shared his experience and knowledge in this field. I would not be as interested in research as I am now if it were not for

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I could not have made it this far without the support of my former chief, Kari Gjelstad. Even if she knew I was going to stop working for her department, she made it clear this project was a big opportunity that could enrich the professional environment of our local psychiatric department. Particular gratitude goes to my two current chiefs, Knut-Erik Hymer, and Tone Nordmark, who gave me the possibility to combine clinical work and research in the department of old age psychiatry of Østfold Hospital Trust. Big thanks go to the administration of the psychiatric clinic of Østfold Hospital Trust, with its former head, Irene Dahl Andersen, and its current head, Andreas Joner. Big thanks also go to the whole department of research of Østfold Hospital Trust. Particularly, I would like to thank my chief of research, Waleed Ghanima, and my two advisors, Hege Karine Jacobsen and Knut Andre Skaug, for all the practical and professional support I received all these years. I would also thank all the members of the research group for mental health of Østfold Hospital Trust, with its former leader, Espen Bjerke, and its current leader, Lynn Mørch-Johnsen, for the professional and friendly support, and for stimulating the research work in our local hospital.

This thesis and my PhD studies could not have been conducted without the professional, practical, and moral support of colleagues, friends, and family. I would like to thank my colleague at the old age psychiatric clinic, Carmen Oelze, whom I consider a mentor in old age psychiatry, and whom I always have had interesting and stimulating clinical discussions with. I would also like to thank her team-member, Hilde Kristiansen, a very experienced nurse whom always supported my work and gave me more insight in the person-centred care of the old patient. Particular thanks go to my team-member, Elin Kolberg Stene, an exceptional geriatric nurse practitioner. Without Elin, it would have been difficult to combine

research and clinical work in a hectic work life. I would like to thank all my other colleagues in the psychiatry department, and in particular the staff at the old age psychiatric unit of Østfold Hospital Trust, for showing professional support and interest in this project. A deep gratitude goes to all the municipalities, nursing home staff, and nursing home physicians who have supported and participated in the RCT study I conducted, together with their residents and their next of kin, whom have been particularly positive to this project. Big thanks also go to Mette Hansen, associate professor at Østfold University College, and her students, for helping with data collection throughout the RCT study. Last, but not least, special thanks go to the administrative staff of the psychiatric clinic of Østfold Hospital Trust, Aina, Lene, Heidi and Birgitte, and to all the librarians of Østfold Hospital Trust, for helping me with all the practical and technical help I needed throughout this whole project.

Work is not everything, but a big part of my life. This research project has undoubtedly influenced my private life and the dearest people I have around me. I would thank my dearest Italian and Norwegian friends, Fabrizio, Marta, Tordbjørn, Julie, Carina and Mikael, my mother Rosella, my father Valerio, and my sister Francesca, for their unconditional support. My very large Norwegian family-in-law has also been an extreme supporter of my work, and has always shown a genuine interest in what I care for professionally. My deepest heartfelt thanks go to my husband Martin. He has always shown genuine interest in my daily work and in this project. He has been attentive to my ups and downs during this challenging work. He has given me space when I needed it, hugs when things were particularly difficult, and helped me finding the right balance between work and private relaxing life. But most of all, I want to thank him for being my life companion, and biggest supporter for almost 20 years.

This project was initially funded by Østfold Hospital Trust, and later it was granted funds by the Norwegian Health Association and The Foundation Dam. Special thanks go to these organizations for giving me the opportunity to carry out this project. Special thanks also go to the local Lions club Skjeberg, which also wished to support and fund my research. Finally I would thank the University of Oslo for accepting my application as a PhD student, and giving me the opportunity to grow both as a researcher and a clinician.

Thesis summary

Dementia is common in nursing home residents. Most residents with dementia experience neuropsychiatric symptoms, such as depression, anxiety, psychosis, and irritability, which may be treated with psychotropic drugs. Psychotropic drugs are commonly categorized as antidepressants, antipsychotics, anxiolytics, sedatives, hypnotics, and antidementia drugs. Older adults and people with dementia should be prescribed psychotropic drugs with cautiousness, as they are particularly sensitive to side effects and may experience severe adverse events. Moreover, the long-term effectiveness of psychotropic drugs to treat neuropsychiatric symptoms may be limited. Therefore, psychosocial and environmental therapies are the first-line approach to treat neuropsychiatric symptoms. Psychotropic drugs are widely used in nursing home residents, but few studies have performed a comprehensive analysis of possible clinical and environmental factors that may explain prescriptions over time. Several psychotropic drugs are defined as potentially inappropriate in older adults, when their risks exceed their benefits. More than 40 structured assessment tools are available to help clinicians identify potentially inappropriate drugs in older adults. The Norwegian General Practice – Nursing Home criteria (NorGeP-NH) is one of three assessment tools defined as specific for nursing home residents. Previous studies have shown that NorGep-NH can detect potentially inappropriate medications in older adults. However, the effectiveness of this tool in a real-world situation has never been tested.

The aim of this thesis was to present prescription patterns of psychotropic drugs in nursing home residents, from admission and over a longer period, and to explore which clinical and environmental characteristics may be associated with psychotropic drugs prescriptions. Further, assuming high prescription rates for psychotropic drugs, and their persistent use, we wanted to test the effectiveness of NorGeP-NH on changing Quality of Life, psychological and physical symptoms, and drug prescriptions in a clinical setting.

Paper 1 and 2 used data collected during a longitudinal study (REDIC-NH) conducted in 47 Norwegian nursing homes. The residents were assessed biannually, from admission and over a maximum period of three years. In paper 1, we presented prevalence, incidence, and persistence rates of psychotropic drugs prescribed in people with dementia at admission, and six months later. We estimated generalized mixed models to explore which clinical and environmental characteristics at admission could explain prescriptions at admission and six months later. Except for antidementia drugs, the prevalence for all the other psychotropic drug categories increased significantly from admission to six-month follow-up. Antidepressants were the most frequently prescribed psychotropic drugs (31.0 % at admission, and 40.1% six months later). Younger residents and residents with more severe

affective symptoms had higher odds of receiving antidepressants. Residents with higher affective symptoms had higher odds of receiving sedatives and hypnotics. Residents with higher comorbidity had lower odds of being prescribed antidepressants. No environmental factors were associated with psychotropic drug prescriptions.

In paper 2, we analyzed prevalence, incidence, and deprescribing rates of psychotropic drugs in residents with and without dementia, from admission up to three-year follow-up. We estimated generalized linear mixed models to analyze which clinical and environmental factors were associated with change in odds of being prescribed psychotropic drugs. People with dementia received most frequently antidepressants (28.5%-42.6%), while residents without dementia received most frequently sedatives and hypnotics (35.4-50.0%). The highest incidence rates, and the highest deprescribing rates (except for sedatives and hypnotics), were found between admission and six-month follow up. Older participants had lower odds of being prescribed antipsychotics and antidepressants throughout the study period, while participants with more severe dementia had lower odds of being prescribed sedatives and hypnotics.

In paper 3, we presented the results of a cluster randomized controlled trial, where we tested the effect of NorGeP-NH on the Quality of Life, mental health, physical health, and prescription rates in nursing home residents, three months after a medication review. Fourteen nursing homes were randomized to intervention (108 residents) and control group (109 residents). We found no statistically significant difference in change in Quality of Life between the two groups. However, Quality of Life remained stable in the intervention group, while it significantly worsened in the control group three months later. We found a statistically significant difference in change in depression scores between intervention group (lower scores), and the control group. We found a temporary significant reduction in the total number of prescribed drugs in the intervention group at eight-weeks, but not at 12-weeks follow-up. We found no difference between the groups in prescriptions of psychotropic drugs, nor significant changes in their daily dosages.

We concluded that psychotropic drugs are largely prescribed in NH residents, already from admission. During the first six months stay there is a dramatic increase in prescriptions for almost all types of psychotropic drugs. Residents with more severe affective symptoms may need particular attention over time, as they are at a higher risk of receiving psychotropic drugs. Further, we found that the NorGeP-NH tool had limited effect on changing Quality of Life and prescription rates (included psychotropic drugs) in nursing home residents. In line with previous studies, medication assessment tools alone may not be as helpful as improving symptoms and medication in nursing home residents.

Sammendrag

Demens forekommer hyppig i sykehjem. De fleste sykehjemsbeboere med demens vil oppleve nevropsykiatriske symptomer i løpet av sykdomsforløpet, som for eksempel depresjon, angst, psykose og irritabilitet. Disse symptomene kan behandles med psykofarmaka. Psykofarmaka er medikamenter som antidepressiva, antipsykotika, angstdempende, beroligende, sove- og antidemensmedisiner. Man bør være forsiktig med å forskrive psykofarmaka til eldre og mennesker med demens, ettersom disse legemidlene kan forårsake alvorlige bivirkninger. Dessuten er effekten av psykofarmaka begrenset når man behandler nevropsykiatriske symptomer. Psykososiale og miljømessige tiltak er derfor førstevalg i behandling av nevropsykiatriske symptomer. Forskrivning av psykofarmaka er vanlig i sykehjem, men få studier har sett på mulige kliniske og miljømessige faktorer som kan forklare forskrivningen over tid. Mange psykofarmaka er potensielt ikke-hensiktsmessige legemidler hos eldre, når risikoen for bivirkninger overstiger den potensielle nytten. Det finnes over 40 strukturerte verktøy som kan hjelpe helsepersonell til å fange opp potensielt ikke-hensiktsmessige legemidler hos eldre. «Norwegian General Practice – Nursing Home» (NorGeP-NH) kriteriene er et av tre verktøy som er spesifikke for eldre sykehjemsbeboere. Tidligere studier har vist at NorGep-NH kan fange opp ikke-hensiktsmessige forskrivninger hos eldre, men effekten av dette verktøyet i klinisk praksis har aldri blitt testet.

Målet med denne avhandlingen var å beskrive hvordan psykofarmaka er forskrevet hos sykehjemsbeboere, fra innleggelse og over tid, og utforske hvilke kliniske og miljømessige faktorer kan være assosiert med forskrivning av psykofarmaka. Videre, ved å anta en høy og persistent forskrivning av psykofarmaka, testet vi effekten av NorGep-NH på livskvalitet, psykologiske og fysiske symptomer, og medikamentforskrivning i sykehjem.

I artikkel 1 og 2 brukte vi data som ble samlet ved en tidligere longitudinell studie (REDIC-NH), gjennomført i 47 norske sykehjem. Sykehjemsbeboerne ble kartlagt to ganger i året, fra innleggelsestidspunkt, og opptil tre år senere. I artikkel 1 presenterte vi prevalens, insidens og persistens for forskrevne psykofarmaka hos mennesker med demens, ved innleggelsestidspunkt og seks måneder senere. Vi estimerte generaliserte mixed models for å utforske hvilke kliniske og miljømessige faktorer ved innleggelsestidspunkt kunne forklare forskrivning av psykofarmaka ved innleggelse og seks måneder senere. Foruten antidemensmedisiner økte forskrivningen av alle psykofarmaka signifikant fra innleggelsestidspunkt til seks måneders senere. Antidepressiva var de hyppigst forskrevne psykofarmaka (31,0 % ved innleggelsestidspunkt, og 40,1 % seks måneder senere). Yngre beboere og beboere med mer alvorlige affektive symptomer hadde høyere odds for å få antidepressiva. Beboere med mer alvorlige affektive symptomer hadde høyere odds for å få

sedativa og hypnotika. Beboere med mere komorbiditet hadde lavere odds for å få antidepressiva. Vi fant ingen miljømessige faktorer assosiert med forskrivning av psykofarmaka.

I artikkel 2 analyserte vi prevalens, insidens og seponeringsrater for psykofarmaka hos beboere med og uten demens, fra innleggelsestidspunkt og over en periode på tre år. Vi estimerte generaliserte lineære mixed models for å analysere hvilke kliniske og miljømessige faktorer som var assosiert med endring i odds for å få forskrevet psykofarmaka. Antidepressiva var oftest forskrevet hos mennesker med demens (28,5 % - 42,6 %), mens sedative og hypnotika var oftest forskrevet hos mennesker uten demens (35,4 % - 50,0 %). Vi fant den høyeste insidensen og den høyeste seponeringsraten (unntatt for sedativa og hypnotika) mellom innleggelsestidspunktet og seks måneders kartlegging. Eldre beboere hadde lavere odds for å få antipsykotika og antidepressiva gjennom hele studien, mens beboere med mer alvorlig grad av demens hadde lavere odds for å få forskrevet sedativa og hypnotika.

I artikkel 3 presenterte vi resultater fra en klyngerandomisert kontrollert studie, der vi testet effekten av en legemiddelgjennomgang utført med NorGeP-NH på livskvalitet, psykisk- og fysisk helse, og medikamentforskrivning hos sykehjemsbeboere, tre måneder etter intervensjonen. Fjorten sykehjem ble randomisert til intervensjons- (108 beboere) og kontrollgruppe (109 beboere). Vi fant ingen statistisk signifikant forskjell i endring på livskvalitet mellom de to gruppene. Imidlertid, forble livskvalitet stabil i intervensjonsgruppen, mens den signifikant forverret seg i kontrollgruppen tre måneder etter intervensjonen. Vi fant en statistisk signifikant forskjell i endring på depresjonsskåre mellom intervensjonsgruppen (lavere skåre), og kontrollgruppen. Vi fant en forbigående signifikant reduksjon i den totale antall forskrevet medikamenter i intervensjonsgruppen ved åtte ukers kartlegging, men ikke ved 12 ukers kartlegging. Vi fant ingen forskjell mellom gruppene hverken i forskrivning av psykofarmaka eller i døgndose.

Vi konkluderte med at psykofarmaka er hyppig forskrevet hos sykehjemsbeboere, allerede ved innleggelsestidspunkt. Vi fant en dramatisk økning i forskrivningen av psykofarmaka de første seks måneders etter sykehjemsinnleggelsen. Beboere med mer alvorlige affektive symptomer bør følges opp ekstra nøye, ettersom de har høy risiko for å bli behandlet med psykofarmaka. Videre fant vi at en legemiddelgjennomgang gjennomført med NorGeP-NH hadde begrenset effekt på livskvalitet og medikamentforskrivning (inkludert psykofarmaka) hos sykehjemsbeboere. I tråd med tidligere studier, er strukturerte legemiddelgjennomgangsverktøy alene ikke nødvendigvis effektive til å forbedre symptomer og legemiddelforskrivning hos sykehjemsbeboere.

List of papers

Paper 1: Callegari E, Šaltytė-Benth J, Selbæk G, Grønnerød C, Bergh S. Does Psychotropic Drug Prescription Change in Nursing Home Patients the First 6 Months After Admission? Journal of the American Medical Directors Association. 2020.

Paper 2: Callegari E, Šaltytė-Benth J, Selbæk G, Grønnerød C, Bergh S. Do prescription rates of psychotropic drugs change over three years from nursing home admission? BMC Geriatrics. 2021.

Paper 3: Callegari E, Šaltytė-Benth J, Selbæk G, Grønnerød C, Bergh S. The effect of the NorGeP-NH on Quality of Life and Drug Prescriptions in Norwegian Nursing Homes: A Randomized Controlled Trial. Pharmacy. 2022.

Abbreviations

ADR Adverse Drug Reaction

ATC The Anatomical Therapeutic Chemical classification system

CDR The Clinical Dementia Rating scale

cNHs Control Nursing Homes

CSDD The Cornell Scale for Depression in Dementia

ICD-10 The International Statistical Classification of Diseases and Health Related Problems – 10th revision

GAI The Geriatric Anxiety Inventory

GMHR The General Medical Health Rating scale

iNHs Intervention Nursing Homes

MADRS The Montgomery and Åsberg Depression Rating Scale

MAOI Monoamine Oxidase Inhibitors

MMSE The Mini-mental State Examination

MOBID-2 The Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale

MoCA The Montreal Cognitive Assessment

NorGeP-NH The Norwegian General Practice – Nursing Home criteria

NPI-NH The Neuropsychiatric Inventory – Nursing Home version

FDG-PET Fluorodeoxyglucose Positron Emission Tomography

PIM Potentially Inappropriate Medication

PRN Pro Re Nata

PSMS The Physical Self-Maintenance Scale

QUALID The Quality of Life in Late-Stage Dementia scale

RCT Randomized Controlled Trial

REDIC-NH The Resource Use and Disease Course in Dementia – Nursing Home study

SD Standard Deviation

SNRI Serotonin and Noradrenaline Reuptake Inhibitors

SPECT Single Photon Emission Computer Tomography

SSRI Selective Serotonin Reuptake Inhibitors

TCA Tricyclic Antidepressants

TUG The “Timed Up & Go” test

1.0 Introduction

Dementia is a syndrome with many possible causes, and characterized by a group of symptoms that occur together. These symptoms are often progressive. People with dementia can present memory impairments, they have difficulties in planning and executing complex tasks, taking care of themselves, and using their language to communicate. Dementia may be caused by several different underlying diseases. Alzheimer's disease is the most common cause of dementia disease. As dementia progresses, the person may require special care, and it is not uncommon that people with dementia are admitted to a nursing home. In Norway, as an example, up to 84% of the patients living in nursing homes have dementia (Helvik et al., 2015). Many people with dementia experience behavioural and psychological symptoms (Helvik et al., 2018). These are referred to as neuropsychiatric symptoms. Depression, anxiety, irritability, aggression, euphoria, sleeping disturbances, delusions, and hallucinations are examples of neuropsychiatric symptoms often experienced by people with dementia.

Psychotropic drugs are a collective name including many types of drugs prescribed to treat mental illnesses, such as depression, anxiety, psychosis, or sleep disturbances. They can be prescribed to treat primary psychiatric disorders (that is, without underlying physical causes) in old patients, but they are also prescribed to treat neuropsychiatric symptoms in people with dementia. Particularly in the latter case, psychotropic drugs seem not to be particularly effective. Yet, they are widely prescribed. This can be problematic as psychotropic drugs may be responsible for several adverse effects, which might worsen an already frail old patient's condition. Common adverse effects can be sedation, cognitive impairment, muscle stiffness, falls, mouth dryness, and extrapyramidal symptoms, such as parkinsonism, akathisia, acute dystonia, or tardive dyskinesia. Paradoxically, they can also give psychiatric symptoms such as e.g., anxiety or depression.

People who are admitted to a nursing home, may continue to receive psychotropic drugs prescribed prior to admission, to mitigate neuropsychiatric symptoms. However, as a resident's disease changes with time, this also may cause important changes in a resident's pharmacotherapy. The longitudinal aspect of drug prescriptions (including psychotropic drugs) is important to understand how these drugs are prescribed over time, and which factors may explain changes in prescriptions in the same person. In Norway, there is no national registry available to keep track of individual prescriptions for residents living in institutions, and no previous study has been conducted in this country to systematically analyse how psychotropic drug prescriptions change in nursing home residents from admission and over a longer period. Similarly, very few international studies have been

conducted in nursing homes to follow up residents from admission, and register systematically how psychotropic drugs are prescribed over a longer period, in relation to clinical symptoms and environmental factors. Therefore, we examined medication data of a longitudinal nursing home study conducted in Norway (REDIC-NH) from 2012 to 2014. In particular, we wanted to see how psychotropic drug prescriptions changed from admission to six months after admission, and further every six months up to three years. We also wanted to see if there were any possible factors, related to either the patients or the nursing home, which could explain changes in prescription rates. This is covered in paper 1 I and paper 2 of this thesis.

Assuming a high prescription rate of psychotropic drugs, we developed a randomized controlled trial aimed to examine if an educational intervention on nursing home personnel could affect the symptoms of nursing home residents and the drugs they were prescribed. Nursing home physicians learned about the management of complex pharmacological treatments in older people, and how to correctly prescribe psychotropic drugs. Further, they learned how to review a medication chart by using a tool called NorGeP-NH. NorGep-NH is a drug chart review list developed to help a nursing home physician by considering tapering or discontinuing a drug therapy in case a particular drug is potentially harmful or inappropriate for older people. NorGeP-NH has not been previously tested in a randomized controlled trial. Even if this tool is not specific for psychotropic drugs, we wanted to see if NorGeP-NH were still useful in a real-world situation, used systematically by nursing home physicians. This is covered in paper 3 of this thesis.

2.0 Background

In this chapter, I will present the most common types of dementia and psychiatric disorders in nursing home residents. I will then present an overview of what psychotropic drugs are, how they are prescribed to older people and in nursing home residents, and the problems related to these drugs. I will also describe polypharmacy and what makes it challenging in a geriatric population. Finally, I will present different methods, including structured drug reviews, to manage polypharmacy in nursing home residents, and what it seems to be effective to reduce unnecessary psychotropic drug prescription. I will also present a short overview of the Norwegian health care system in relation to the care of older people.

2.1 Dementia

2.1.1 Definition, prevalence, and incidence of dementia

Dementia is a syndrome characterized by cognitive impairment, loss of function and behavioural symptoms such as impairment in emotional control, motivation, and social behaviour (Table 2.1.1.1) (World Health Organization, 2004). Dementia is acquired, chronic and usually progressive. Dementia may be caused by several underlying diseases, as neurodegenerative disorders, cerebrovascular disease, infections, and substance abuse. Even if dementia is considered a neurological disorder, it virtually always presents at least one psychiatric or behavioural symptom during the disease (Selbaek et al., 2014; Vik-Mo et al., 2018). When speaking about neuropsychiatric symptoms in the context of dementia, the terms *Behavioural and Psychological Symptoms in Dementia* or *neuropsychiatric symptoms* are used interchangeably. In this thesis, I will use the term neuropsychiatric symptoms, and I will discuss this aspect later in chapter 2.1.3.

It is estimated that 55.1 million people have dementia worldwide, and about 14.1 million reside in Europe (World Health Organization, 2021). Dementia is the seventh leading cause of death, and due to population growth and increased longevity, it has been estimated that in 10 years, 78 million people will have dementia worldwide, increasing to 139 million people in about 30 years (World Health Organization, 2021). In 2015, it was estimated that about 9.9 million new cases of dementia were diagnosed worldwide every year, with a 30% increase from a previous report three years before (Prince et al., 2015). In Norway, 14.6% among people 70 years of age or older have dementia, and Alzheimer's disease represents over half of all the cases (57%) (Gjøra et al., 2021). It is estimated that in Norway, about 101,000 people had dementia in 2020, and in 30 years, there will be a 130% increase in cases (about 237,000) (Gjøra et al., 2021).

Table 2.1.1.1 Diagnostic criteria of dementia according to ICD-10

Criteria	Description
1	1.1 Decline in memory, for both verbal and non-verbal material 2.0 Decline in other cognitive abilities such as deterioration in judgement and thinking, planning, and organizing, and general processing of information.
2	Preserved awareness of the environment.
3	Decline in emotional control or motivation, or change in social behaviour with at least one of the following: 3.1 Emotional lability 3.2 Irritability 3.3 Apathy 3.4 Coarsening of social behaviour
4	Criterion 1 should have been present for at least six months.

In most of the cases dementia worsens with time, and people with dementia will often need an increased level of daily care. It is not uncommon that people with dementia in the end will be admitted to a nursing home. A Norwegian study followed 2,938 patients with dementia living at home. During a follow-up of almost 11 years, 34% of the patients were admitted to a nursing home (Mjørud et al., 2020). There are several factors increasing the risk of nursing home admission: behavioural and psychological symptoms associated to dementia, a worsening in cognitive impairment, and a reduction in the level of daily functioning (Toot et al., 2017). Although it is difficult to compare studies from different countries due to different health care systems, there is an overall high prevalence of people with dementia living in nursing homes. In the UK for example, 77% of the patients living in nursing homes had dementia, while in Norway the prevalence was 84.3% (Helvik et al., 2015; Stewart et al., 2014).

2.1.2 Dementia subtypes

Five subtypes represent over 95% of all types of dementia: Alzheimer's disease, vascular dementia, Lewy body dementia, Parkinson's disease dementia, and Frontotemporal dementia (Wu et al., 2018).

Alzheimer's disease is the most common cause of dementia (between 60% and 80% of all cases) (Gauthier et al., 2021). It is a neurodegenerative disorder in which two mechanisms in the brain seem to play an important role, causing neuronal damage and death: the accumulation of the protein amyloid beta, forming plaques, and the deposit of neurofibrillary tangles inside neurons. The degeneration often starts in the temporal lobes of the brain, moving further into the parietal lobes and afterwards disseminating all over the brain. Typical symptoms are memory loss, difficulties in learning new information, disorientation, and

language difficulties (Scheltens et al., 2016). As the disease progresses, a person with Alzheimer's disease will experience movement problems, such as difficulties in coordinating complex movements, loss of control of bodily functions, and a decreased ability of self-care (Tarawneh & Holtzman, 2012).

Cerebrovascular disease is the second most common cause of dementia (Gjøra et al., 2021). The large variation in the types of neurovascular damage in the brain often gives a very wide range of symptoms that may have many similarities with Alzheimer's disease. The damage may occur after a cerebral infarction, a brain haemorrhage, or a disease that occurs in the small brain vessels, causing poor oxygenation and nerve damage over time. This leads to a distinction in the ICD-10 between multi-infract dementia (caused by one or several ischaemic episodes), subcortical vascular dementia (caused by lesions in the deep white brain matter), and a combination of these two. It is common for people with a vascular dementia to have memory loss (World Health Organization, 1993). People with vascular dementia may have difficulties in processing information rapidly, recalling lists of words or visual content, and have impaired executive functions, including thinking, planning, executing, stopping, and judging an action (Iadecola et al., 2019).

Lewy body dementia is caused by the deposit of alfa-synuclein protein (called Lewy bodies) inside neurons, causing toxicity, nerve damage, and death (Walker et al., 2015). Lewy body dementia may present itself with two different clinical manifestations: dementia with Lewy bodies, and Parkinson's disease dementia, as the underlying mechanisms are very similar, although the temporal presentation of symptoms, and the consequent diagnosis, is different (McKeith et al., 2017; Walker et al., 2015). In case dementia develops within one year from the onset of spontaneous parkinsonism, the diagnosis dementia with Lewy bodies should be made; in case dementia develops after Parkinson's disease is well established, the diagnosis Parkinson's disease dementia should be made (Walker et al., 2015)

People with dementia with Lewy bodies do not always present a clear memory loss to begin with. Other symptoms, such as executive problems or disorientation, movement disorders (parkinsonism) together with visual hallucination and sleep disturbances may me predominant. A list of diagnostic criteria is presented in table 2.1.2.1 (McKeith et al., 2017).

Table 2.1.2.1 Diagnostic criteria of dementia with Lewy bodies (from McKeith, Boeve et al. 2017)

Possible diagnosis: one core feature with no biomarkers OR no core feature and one or more biomarkers **Probable diagnosis**: two or more core features with or without biomarkers OR one core feature and one or more biomarkers	**Central features**	Progressive dementia leading to impairment in social and occupational function
		Impairment in attention, executive and visuospatial functions may occur early; memory impairment may not occur in early stages
	Core features	Fluctuations in cognition
		Recurrent visual hallucinations
		Rapid eye movement (REM) sleep disorder
		Spontaneous parkinsonism symptoms (one or more): bradykinesia, rest tremor, rigidity
	Suggestive features .	Severe sensitivity to antipsychotics
		Postural instability
		Repeated falls
		Syncope or transient episodes of unresponsiveness
		Severe autonomic dysfunction
		Hallucinations in other modalities
		Systematized delusions
		Apathy, anxiety, depression
	Indicative biomarkers	Reduced dopamine transporter uptake in basal ganglia (by SPECT or PET)
		Abnormal myocardial scintigraphy
		REM sleep without atonia by polysomnography
	Supportive biomarkers	Medial temporal lobe structures (by CT/MRI scan) preserved
		Generalized low uptake on SPECT/PET perfusion/metabolism, reduced occipital activity with or without cingulate island sign on FDG-PET
		Prominent posterior slow-wave activity on EEG and periodic fluctuations in the pre-alpha/theta range

One last cause of dementia worth mentioning is frontotemporal dementia. This is an "umbrella term", including a heterogeneous group of syndromes caused by the neurodegeneration of the frontal and/or temporal brain lobes. From a clinical perspective, frontotemporal dementia can present itself with three different variants: behavioural-variant frontotemporal dementia, non-fluent variant primary progressive aphasia, and semantic variant primary progressive aphasia (Younes & Miller, 2020). These syndromes occur at an earlier age compared to other forms of dementia (Younes & Miller, 2020). While the two types of primary progressive aphasia are easier to recognize due to the presence of language impairment, the behavioural variant is diagnostically challenging to recognize, as it often is misdiagnosed as a psychiatric disorder. Frontotemporal dementias can in fact

present personality changes with disinhibition, compulsive behaviour and loss of empathy, depression, apathy, psychosis, and hyperorality, leading the physician to misinterpret symptoms (Younes & Miller, 2020).

There are several other causes of dementia, which are reported schematically in table 2.1.2.2. It is important to notice that the causes of dementia are not mutually exclusive. As a person gets older, different pathologies may occur in the brain at the same time, increasing the risk of various forms of dementia. Dementia can therefore present itself with a very wide range of symptoms, according to the type of pathology contributing to the neuronal damage (James & Bennett, 2019; Kapasi et al., 2017).

Table 2.1.2.2 Possible causes of dementia. Inspired by Gauthier and colleagues (Gauthier et al., 2021).

Neurodegenerative disorders	Alzheimer's disease
	Lewy body disease
	Parkinson's disease
	Frontotemporal degeneration / dementia
	Huntington's chorea
	Progressive supranuclear palsy
	Corticobasal degeneration
Cerebrovascular disease	Multi-infarct dementia
	Subcortical vascular dementia
	Cerebral amyloid angiopathy
Infections	Neurosyphilis
	Encephalitis
	Prion disease
	HIV
Other causes	Wilson's disease
	Normal pressure hydrocephalus

2.1.3 Neuropsychiatric symptoms in people with dementia

Neuropsychiatric symptoms range from psychiatric symptoms such as depression, anxiety, hallucinations, delusions, and euphoria, to behavioural disturbances such as agitation, aggression, apathy, disinhibition, aberrant motor behaviour, night-time behaviour, irritability, and changes in eating behaviour. Neuropsychiatric symptoms are a common cause of admission to a nursing home (Toot et al., 2017). Neuropsychiatric symptoms often fluctuate during dementia, and they seem to be associated with multiple factors. They can be triggered by aspects related to the person with dementia, such as medical problems, previous psychiatric history, or unmet needs; the person's caregiver, such as high level of burden or mismatch between the caregiver and the patient; or the environment the person lives in, such

as over- or under-stimulation or not appropriately structured / customized activities (Ferreira et al., 2020; Kales et al., 2015). In some cases, neuropsychiatric symptoms and factors that influence neuropsychiatric symptoms have a mutual negative influence. As an example, aggression in a patient may over time increase the level of burden in the caregivers, which, in turn, may reduce the quality of the caregiving, and increases the aggressive behaviour in the patient (Berger et al., 2005; Kolanowski et al., 2017). The frequency and prevalence of neuropsychiatric symptoms in people with dementia vary between countries and according to which study is considered. However, depression, anxiety, irritability, agitation, psychosis, and apathy are highly prevalent (Helvik et al., 2018; Leung et al., 2021; Selbæk et al., 2013; Vik-Mo et al., 2018).

The management of neuropsychiatric symptoms is classically divided into pharmacological and non-pharmacological. The first is presented in chapter 2.3.3 of this thesis. The nomenclature of non-pharmacological treatments is debated, and no consensus is reached on how these may be categorized. They usually tend to be based on psychosocial and environmental models, and are generally named psychosocial treatments, either focusing on the behaviour of the patient, on the environment a patient is exposed to, or by supporting a patient's next of kin, caregivers, or physicians (Kales et al., 2015). Table 2.1.3.1 reports a few examples of non-pharmacological therapies targeting neuropsychiatric symptoms (de Oliveira et al., 2015; Dyer et al., 2018; Kales et al., 2015). In this text I will use non-pharmacological treatment and psychosocial treatment as synonyms.

Table 2.1.3.1. Examples of psychosocial and environmental therapies targeting neuropsychiatric symptoms.

Type of approach	Explanation
Cognitive training	Structured programs to improve memory and level of functioning
Reminiscence therapy	The person discuss past life experiences with the caregiver
Simulated presence therapy	The person is exposed to recorded voices of family members
Music therapy	Various activities where music (either live or recorded) is the main intervention
Aromatherapy	The person is exposed to aromatic oils diffused in the environment
Light therapy	The person is exposed to bright light for a determined period during the day
Physical exercise	Structured programs where physical activities are the main intervention

The psychosocial and environmental management of neuropsychiatric symptoms is considered first-line treatment and it often requires a complex approach. What may work for one patient, does not necessarily work for another (Kales et al., 2015). It is not uncommon that interventions on several levels are necessary to target neuropsychiatric symptoms. Educating and supporting family members and other caregivers on how to communicate with

the patient, how to customize the daily activities level and environment a patient lives in, seem to show the strongest evidence of efficacy (Gerlach & Kales, 2020; Preuss et al., 2016; Trivedi et al., 2019). Systematic interdisciplinary approaches, such as *Targeted Interdisciplinary Model for Evaluation and treatment of neuropsychiatric symptoms* (TIME) or the *Describe, Investigate, Create, Evaluate* (DICE) approach may be helpful tools to manage neuropsychiatric symptoms (Kales et al., 2014; Lichtwarck et al., 2018). Nevertheless, neuropsychiatric symptoms still remain one of the biggest challenges in dementia care (Kales et al., 2014), and have a clear negative impact on a person's Quality of Life (Burks et al., 2021).

2.2 Psychiatric disorders in people living in nursing homes

In the previous chapter, I presented neuropsychiatric symptoms in the context of dementia. However, nursing home residents may also have primary psychiatric disorders, such as depression, anxiety, or psychosis. These disorders may be present with or without dementia. In case a person has dementia, a primary psychiatric disorder should be understood as such when dementia is not a plausible cause of the disorder, but rather a comorbid disease. As an example, psychosis can be understood as primary, when no other underlying causes can explain the syndrome, or secondary, when psychosis is caused by a somatic disease, such as dementia. Depression may be understood as a neuropsychiatric symptom in the context of dementia, or as a primary psychiatric disorder when symptoms are so severe that the diagnostic criteria for depressive disorder are fulfilled, making depression a comorbid independent syndrome. However, this distinction may be difficult to make in a clinical context. In the next chapters, I will present the most common features of depression, anxiety, and psychosis as psychiatric disorders in nursing home residents. Later in this thesis, when referring to depression, anxiety, or psychosis, I will often consider them as neuropsychiatric symptoms.

2.2.1 Depression

Depression is a syndrome characterized by three core criteria: lowering of the mood, reduction of energy, and decrease in activity (World Health Organization, 2004). Additional criteria can be part of a depression (Table 2.2.1.1) and according to how many and how intense the symptoms are, depression can be defined as mild, moderate, or severe. The term depression is often used to refer to the clinical syndrome called major depressive disorder, but depression can also be used as a synonym of sadness or depressed mood, that is as a symptom.

Table 2.2.1.1 Criteria for major depressive disorder according to ICD-10.

Core criteria	Lowering of the mood
	Reduction of energy
	Decrease in activity
Additional criteria	Reduced capacity for enjoyment and interest
	Reduced capacity to concentrate
	Marked tiredness
	Reduced confidence or self-esteem
	Ideas of guilt and worthlessness
	Recurrent thoughts of death or suicide
	Diminished ability to think/concentrate or indecisiveness
	Psychomotor agitation or retardation
	Sleep disturbance
	Loss of libido
	Change in appetite with weight change

In the general older population, depression is a frequent mental illness, ranging from 12.3% in people 60-64 years of age to 20.9% in people 86-90 years of age (Solhaug et al., 2012). Depression is also a common disease found in patients newly admitted to a nursing home (25-26%) (Iden et al., 2014; Ulbricht et al., 2017), and in people with dementia, depression increases the risk of nursing home admission (Toot et al., 2017). Several authors have argued that it may be challenging to diagnose depression in older adults. Older adults with depression can in fact present less severe or less specific symptoms, such as sleeping problems, difficulties in concentrating, weight loss, and unspecific physical symptoms / pain. In the case of people with dementia, it might be even more difficult to get an accurate report from the patient (Barca et al., 2009; Burke et al., 2019). In addition, symptoms of depression may overlap with symptoms found in dementia, such as apathy, anxiety, or cognitive dysfunction (Burke et al., 2019). Considering that most nursing home residents have dementia (Helvik et al., 2015), the diagnostic and therapeutic approach of depression can be challenging. In addition, depression in late life seems to have a different pathogenesis compared to younger adults. Different models have been presented as possible causes of depression in the older adult. The depression-executive dysfunction syndrome, cerebrovascular disease, amyloid beta accumulation and inflammatory changes have all been discusses as possible underlying mechanisms for the development of depression in older adults, and show the complexity of an aging brain (Alexopoulos, 2019). Several assessment tools have been developed and validated to identify possible depressive

symptoms in older adults. The Geriatric Depression Scale (van Marwijk et al., 1995), the Cornell Scale for Depression in Dementia (Alexopoulos et al., 1988), and the Neuropsychiatric Inventory (Cummings et al., 1994) are examples of such tools. About 20 years ago, an expert panel presented a new set of criteria to diagnose depression in people with Alzheimer's disease (NIMH-dAD) (Olin et al., 2002). These criteria took inspiration from the criteria for major depressive disorder found in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatry Association, 2013), but did not take into consideration subjective verbal expression of symptoms or cognitive symptoms, and needed less symptoms to be present for a shorter period in order to set the diagnosis (Olin et al., 2003). This set of criteria was able to identify a greater number of patients with Alzheimer's disease and depression compared to other criteria (Teng et al., 2008) and can be useful in a clinical practice.

2.2.2 Anxiety

Anxiety symptoms can be a normal and physiological reaction to a known or unknown threat (Steimer, 2002). However, when anxiety becomes so severe in relation to a threat or a stressful cause, to the point of interfering with a person's daily life, it can become pathological (Steimer, 2002). Anxiety disorders have a wide variation in how they clinically present themselves, ranging from phobias, panic disorders, to more generalized anxiety. Symptoms associated with anxiety often vary according to the cause and severity of the anxiety. They can range from nervousness, psychological restlessness, or a sense of imminent danger, to more physical symptoms, such as trembling, sweating, palpitations, blurred vision, or nausea. In community-dwelling persons 65 years of age or older, specific phobias and generalized anxiety disorders are the most common anxiety disorders (11.5% and 6.9% respectively) (Kirmizioglu et al., 2009). However, up to 20% of older people living in nursing homes suffer from anxiety disorders, where specific phobias and generalized anxiety disorders have highest prevalence rates, as a recent systematic review showed (Creighton et al., 2016). Anxiety symptoms can also be found in other psychiatric disorders, such as depression or dementia. When considering anxiety as a group of symptoms, its prevalence in older residents living in nursing homes increases up to 58.4% (Creighton et al., 2016). There are several correlated factors to anxiety. As an example, depression, a family history of depression, and functional decline are highly correlated to generalized anxiety disorder (Gonçalves et al., 2011). Anxiety in older people has also been found associated with the use of antidepressants/lithium, pain, and increased psychosocial burden because of lower perceived Quality of Life and social support (Creighton et al., 2017).

2.2.3 Psychosis

A very broad definition of psychosis is the loss of contact with reality (Arciniegas, 2015). Psychosis can present with delusions, hallucinations, disorganized thoughts, negative symptoms (such as apathy, inadequate speech or emotional response) (World Health Organization, 1993), or a combination of these (Arciniegas, 2015). In the older population, psychosis is common in both community-dwelling persons (27%) and in nursing home residents (62%) (Reinhardt & Cohen, 2015). In older people it is particularly important to recognize the causes of the psychosis, as secondary psychosis (that is, psychosis not induced by schizophrenia or a mood disorder as an example) represents the majority of the cases (Tampi et al., 2019). Psychosis in the older patient can in fact be caused by delirium, medications as antiparkinsonian or anticholinergic medication, several medical conditions (neurological, endocrine/metabolic disorders or infections as an example), and dementia (Reinhardt & Cohen, 2015). In people with Alzheimer's disease, psychotic symptoms are fairly common (median prevalence 41.1%), with delusions being more frequent than hallucinations (Ropacki & Jeste, 2005). A recent paper reviewing psychosis in Alzheimer's disease, showed that common symptoms are delusions of theft, infidelity, abandonment, misidentification (for example the idea that someone close to the patient is an impostor), or visual hallucinations (Ballard et al., 2020). In a recent longitudinal study conducted in Norwegian nursing homes, the prevalence of delusions ranged from 18.5% to 22.5%, while the prevalence of hallucinations ranged between 5.0% and 10.4% (Helvik et al., 2018).

2.3 Psychotropic drugs

2.3.1 Definition and types of psychotropic drugs

The term "Psychotropic drugs" refers to a wide range of prescription drugs commonly used to treat primary psychiatric disorders. They can be roughly divided in two big categories: psycholeptic drugs, which have a calming effect, and psychoanaleptic drugs, with a stimulant effect. Even though this classification can be found in the Anatomical Therapeutic Chemical (ATC) classification system, it might be considered reductive and too simple compared to the effect of each psychotropic drug and their neurochemical mechanisms.

Psycholeptic drugs include antipsychotics, anxiolytics, hypnotics, and sedatives. Antipsychotics are drugs prescribed to treat psychosis. They can be divided into two groups: first generation (typical) and second generation (atypical) antipsychotics. This classification is mainly made to emphasize when in time they were discovered, and the fact that second generation antipsychotics give considerable less side effects at therapeutic dosages compared to first generation antipsychotics (Marder et al., 2009). Antipsychotics act on

different brain receptors, controlling several neurotransmitters, such as dopamine, serotonin, or noradrenaline. While the main action of typical antipsychotics is on dopamine brain receptors, atypical antipsychotics also have a high affinity for serotonin receptors (Gareri et al., 2014; Marder et al., 2009; vanKammen et al., 2009). Anxiolytics include different drugs prescribed to treat anxiety, both as a symptom and as a disorder. It is a group of drugs with very different mechanisms of action. Among these, the most known drugs are benzodiazepines. Sedatives and hypnotics are drugs that have a calming effect and induce sleep, respectively. Hypnotics are popularly called “sleeping pills”. Also in this category, we find drugs that have different mechanisms of action. Among these, the most prescribed hypnotic in Norway in 2020, both in the general population and in people older than 65 years, is a benzodiazepine-like drug called zopiclone (Norwegian Institute of Public Health, 2021).

Psychoanaleptic drugs include antidepressants, psychostimulants, and anti-dementia drugs. Antidepressants are divided into different categories according to their mechanism of action. Most antidepressants act on different neurotransmitters in the brain such as serotonin, noradrenaline, and dopamine. The first antidepressants that were discovered in the 1950s were called monoamine oxidase inhibitors (MAOI) (Sussman, 2009a), and their action did not specifically target one particular neurotransmitter, as they act on the level of dopamine, serotonin, and noradrenaline. Tricyclic antidepressants (TCA), also discovered in the 1950s, take their name from their chemical structure (tricyclic = “three rings”) and are more selective, acting mainly on serotonin and noradrenaline levels in the brain (Sussman, 2009a). A new class of antidepressants were further discovered, called Selective Serotonin Reuptake Inhibitors (SSRI), which work selectively on the serotonin levels in the brain (Sussman, 2009b). In the same way, Serotonin-Noradrenaline Reuptake Inhibitors act specifically on serotonin and noradrenaline levels in the brain (Thase, 2009b). In 2020, SSRI were the most prescribed types of antidepressants in Norway, both in the general population and in patients 65 years of age or older (Norwegian Institute of Public Health, 2021). This probably reflects the fact that SSRI are still considered the first line treatment for both major depressive disorders and anxiety disorders in national and international guidelines (National Institute for Health and Care Excellence, 2009; Norwegian Directorate of Health, 2009). In the recent years, a new generation of antidepressants has been approved for clinical use. They are classified as “other antidepressants” in the ATC classification system, and they have a very variated mechanism of action. Bupropion, for example, acts on dopamine and noradrenaline levels in the brain (DeBattista & Scatzberg, 2009); mirtazapine (a tetracyclic = “four rings” antidepressant) increases the activity of noradrenergic and serotonergic neurons (Thase, 2009a), while vortioxetine seems to modulate, more than increase, the level of serotonin in the brain and is well tolerated (Jacobsen et al., 2015). Recently, a known drug previously

used as a tranquilizer / anaesthetic, called ketamine, has shown promising results in the treatment of therapy-resistant depression (McIntyre et al., 2020).

Psychostimulants are drugs mainly used to treat ADD (Attention Deficit Disorder) or AD/HD (Attention Disorder / Hyperactivity Disorder). Methylphenidate, amphetamine, and amphetamine derivatives are examples of these drugs.

Antidementia drugs are classified into cholinesterase inhibitors and memantine, and they are used to treat symptoms connected to some types of dementia (O'Brien et al., 2017). In Norway, these drugs are approved to treat Alzheimer's disease, dementia with Lewy bodies, and Parkinson's disease dementia (Norwegian Directorate of Health, 2017). The main action of cholinesterase inhibitors is to reduce the breakdown of acetylcholine in the synaptic cleft, an important neurotransmitter involved in enhancing cognitive function (Parsons et al., 2013; Walczak-Nowicka Ł & Herbet, 2021). The main action of memantine is to modulate the activity of glutamate-neurones (pathologically overstimulated in Alzheimer's dementia), being memantine a N-methyl-D-Aspartate (NMDA) receptor antagonist (Parsons et al., 2013). The NMDA receptors are a subgroup of receptor that control the glutamate-mediated excitatory signals in the central nervous system, being glutamate the most common excitatory neurotransmitter in the brain (Wang & Reddy, 2017).

When referring to psycholeptics and psychoanaleptics, other drugs used to treat psychiatric disorders are left out, as they are classified under other categories in the ATC classification system. However, it is important to mention that some antiepileptics are commonly used to treat depression or manic disorders in people with bipolar affective disorder. Lamotrigine for instance, is used alone, or in combination with other psychotropic drugs, to treat bipolar depressions (Besag et al., 2021); valproate on the other hand, is a valid anti-manic agent (Kishi et al., 2021).

Finally, lithium, although it is classified in the antipsychotics ATC classification system, should be considered a drug of its own. It is used to treat bipolar affective disorder (Kishi et al., 2021), and can be used as an augmenting agent to treat therapy-resistant depressions (Strawbridge et al., 2019). (Lewitzka et al., 2015)

2.3.2 Adverse effects of psychotropic drugs in older people

Homeostasis ("homeo" = similar and "stasis" = standing still) refers to the body's ability to keep a physiological internal balance. Older people have a lower ability to preserve homeostasis when their body is exposed to stress. When administering a psychotropic drug, its effect may show not only in the central nervous system, but also in the peripheral nervous system. The main target of psychotropic drugs is receptors in the brain, but the same receptors are also found in the spinal cord, in peripheral nerves, and in other organs. This

gives an increased risk of adverse reactions that need to be considered. Older people are more susceptible to these adverse events, which may cause severe consequences compared to younger adults. This is not only related to psychotropic drugs, although this chapter will only focus on this drug category.

Pharmacokinetics, which is how a drug is handled by the body, presents different changes in an ageing body. Blood flow through the liver decreases, leading to a slower drug metabolism (Mangoni & Jackson, 2004). Similarly, renal filtration may be reduced, leading to an accumulation of drugs that are usually excreted via the kidneys. This is particularly important for drugs with a narrow therapeutic window, such as lithium (Mangoni & Jackson, 2004). An older body has in general an increased body fat : body water ratio, which leads to an increased half-life and risk of side effects for drugs that are liposoluble, like most psychotropic drugs (Mangoni & Jackson, 2004).

Pharmacodynamics, which is how a drug acts on the body, also changes in an older body. It might be difficult to generalize which pharmacodynamic changes are present in an old patient, due to a high variation in sensitivity, response, and pharmacokinetics. As an example, some authors have proposed that changes in receptor expression, concentration of neurotransmitters and permeability of the blood-brain-barrier might all be involved in modifying the sensitivity of drugs in older people (Drenth-van Maanen et al., 2020). Because of this, older patients seem to be more sensitive to psychotropic drugs and respond with a higher rate of adverse effects. As an example, an aging brain is more sensitive to the effect of benzodiazepines, leading to sedation, postural sway, and memory impairment (Drenth-van Maanen et al., 2020; Mangoni & Jackson, 2004). Antipsychotics, administered alone or combined with other sedative drugs, may cause oversedation, and they have been shown to increase the risk of falls, cerebrovascular events, prolonged QT interval, worsening of motor symptoms such as tardive dyskinesia or extrapyramidal effects, and death (Davies & O'Mahony, 2015; Glass et al., 2020).

Although newer antidepressants are considered relatively safe in the old population, SSRI and SNRI seem to be associated to an increased risk of falls, fracture, and mortality (Sobieraj et al., 2019). Citalopram and escitalopram are mentioned among the first pharmacological choices in the treatment of late-life depression (Beyer & Johnson, 2018; Mulsant et al., 2014), but citalopram was associated to an increased QT interval in people with Alzheimer’s disease receiving 30mg citalopram daily (Drye et al., 2014). Antidepressants may also increase the risk of gastrointestinal bleeding, particularly in patients taking serotonin reuptake inhibitors (Coupland et al., 2011). This is of particular concern if a patient is already taking anticoagulants. It has been suggested that SSRI/SNRI

may worsen motor symptoms in Parkinson's disease (Pontone & Mills, 2021), and serotonergic antidepressants in general may increase the risk of extrapyramidal reactions, although most of the reported studies refer to case reports, and their results should be interpreted cautiously (Hawthorne & Caley, 2015).

Some psychotropic drugs are known to give anticholinergic side effects. This happens when a drug binds to muscarinic receptor in the central and peripheral nervous system, blocking neurotransmission with acetylcholine. This neurotransmitter is involved in important central nervous system functions, such as memory, attention, and learning, and signal transmission in the peripheral nervous system, controlling bladder, intestine and heart function. The anticholinergic effect of psychotropic drugs may lead to a wide series of adverse events such as confusion and cognitive impairment, psychosis, dry mouth, constipation, and urinary retention (López-Álvarez et al., 2019). Psychotropic drugs known to have a high anticholinergic load are some TCA such as clomipramine, imipramine, and amitriptyline; the typical antipsychotics perphenazine, haloperidol, and levomepromazine; or some atypical antipsychotics such as clozapine and olanzapine (López-Álvarez et al., 2019; Reiter et al., 2021). It is important to mention that some anticholinergic effects may mimic neuropsychiatric symptoms, such as psychosis, that are also common in people with dementia or in primary psychiatric disorders, leading the physician to think there is a need to increase the dosage of the psychotropic drug, which in reality causes the adverse effect (López-Álvarez et al., 2019; Mihanović et al., 2009).

2.3.3 Psychotropic drugs in the treatment of dementia-related neuropsychiatric symptoms

It is important to mention that psychotropic drugs are not considered first-choice treatment to manage neuropsychiatric symptoms (Kales et al., 2015), but psychotropic drugs can still be used in the management of these symptoms. This chapter will summarize the efficacy and safety issued concerning the most relevant psychotropic drug category to treat neuropsychiatric symptoms, by considering recent literature.

2.3.3.1 Antipsychotics

Antipsychotics are widely used to treat neuropsychiatric symptoms, both in the presence of hallucinations, delusions, agitation, and aggression. They have in fact been proposed as a pharmacological first-choice in emergent and urgent neuropsychiatric symptoms (Chen et al., 2021). In Norway, risperidone is approved as a short-term treatment option against agitation in moderate / severe Alzheimer's dementia (Statens legemiddelverk, 2020), while haloperidol is approved to treat psychosis and persistent aggression in patients with moderate / severe Alzheimer's dementia and vascular dementia (Statens legemiddelverk, 2019). However, the

use of haloperidol in older people rises several concerns, due to its adverse reaction profile, particularly associated with acute parkinsonism, akathisia, hyperprolactinemia, and malignant neuroleptic syndrome (Solmi et al., 2017). Additionally, haloperidol causes more severe extrapyramidal symptomes compared to second-generation antipsychotics (Boettger et al., 2015; Klemp et al., 2011), and it is associated to a higher mortality risk compared to atypical antipsychotics in nursing home residents with dementia (Liperoti et al., 2009). A recent network meta-analysis showed that among atypical antipsychotics, no drug showed to be better than others in respect of safety and effectiveness; however, among aripiprazole, quetiapine, risperidone, and olanzapine, only aripiprazole was associated with an improvement in neuropsychiatric symptoms measured with the Neuropsychiatric Inventory, compared to placebo (Yunusa et al., 2019). Risperidone has also been shown to be more effective than placebo to treat agitation (Kongpakwattana et al., 2018). These results are in line with a previous systematic review of meta-analyses, that showed how atypical antipsychotics, in particular risperidone, olanzapine and aripiprazole, were effective to treat neuropsychiatric symptoms, such as psychosis, aggression and agitation (Tampi et al., 2016). The use of antipsychotics in people with dementia has several safety concerns. A recent meta-analysis presents how antipsychotics increase the risk of cerebrovascular events compared to placebo, and compared to antidepressants, they are associated with a higher mortality risk (Watt et al., 2020). This is in line with a previous systematic review of meta-analysis, that showed how antipsychotics are associated to a greater risk of adverse effects, included cerebrovascular events and death, compared to placebo (Tampi et al., 2016). Risk of fractures increased when patients used antipsychotics compared to anticonvulsants, but the risk decreased when patients were prescribed antipsychotics compared to cholinesterase inhibitors alone or combined with memantine (Watt et al., 2020). Antipsychotics may be effective to treat neuropsychiatric symptoms, but they should be used cautiously due to the increased risk of adverse effects and are only recommended, for the shortest possible time, when neuropsychiatric symptoms are severe and when neuropsychiatric symptoms do not respond to other non-pharmacological treatments (Tampi et al., 2020).

It is worth mentioning that in case of psychotic symptoms in people with dementia with Lewy bodies and Parkinson's disease dementia, clozapine and pimavanserin (the latter not approved in Norway) have shown favourable results (Ford & Almeida, 2020; Iketani et al., 2020; Zhang et al., 2019). Other atypical antipsychotics, such as olanzapine, aripiprazole, or risperidone, have shown doubtful efficacy or more severe side effects, such as motoric deterioration (Kyle & Bronstein, 2020)

2.3.3.2 Antidepressants

In presence of depressive symptoms or major depressive disorder in people with dementia, antidepressants may be prescribed. A double-blind, randomized placebo-controlled trial, for example, showed that depression in nursing home patients with dementia, without a history of depressive disorder, worsened after discontinuation of four different SSRI (escitalopram, citalopram, sertraline, and fluoxetine) (Bergh et al., 2012). However, a Cochrane meta-analysis showed neither strong evidence of efficacy of antidepressants on depression in people with dementia, nor sufficient evidence to state if specific antidepressants could have a favourable effect on depression on particular subtypes of dementia (Dudas et al., 2018). On the other hand, antidepressants have been suggested as medication useful in managing other neuropsychiatric symptoms than depression. The CitAD Randomized Clinical Trial, for example, showed that citalopram was effective in reducing agitation, but caused a series of side effects of concern, such as more increased falls, gastrointestinal symptoms, cognitive worsening, and prolonged QTc interval (Porsteinsson et al., 2014). In particular, the subgroup of participants living at home, who had milder cognitive impairment and a "moderate" to "moderately-severe" agitation scores seemed to benefit of citalopram the most (Schneider et al., 2016). Similar results were obtained by network meta-analysis, showing that SSRI as a group had a greater efficacy than placebo to treat agitation in people with dementia (Kongpakwattana et al., 2018). A recent meta-analysis showed contrasting findings when comparing its results with previous studies: antidepressants with a serotonergic effect seem to improve agitation and overall neuropsychiatric symptoms, and they may also be effective to manage depressive symptoms, and improve cognition (Hsu et al., 2021). Antidepressants were found to be the safest treatment with respect to risk of cerebrovascular events (Watt et al., 2020), and serotonergic antidepressants were well tolerated when used to treat neuropsychiatric symptoms in dementia (Hsu et al., 2021). In Norway, however, antidepressants are not approved to treat agitation in people with dementia (Felleskatalogen AS, 2022).

2.3.3.3 Antidementia drugs

Guidelines state that cholinesterase inhibitors and memantine should be prescribed to people with dementia, as they may enhance cognitive function and delay the worsening of symptoms (Parsons et al., 2013; Walczak-Nowicka Ł & Herbet, 2021). Both cholinesterase inhibitors and memantine together may have a synergic effect in the treatment of Alzheimer's dementia, due to their different mechanisms of action (Parsons et al., 2013). However, a recent meta-analysis of 142 studies showed that only donepezil was likely to give a significant improvement in cognitive function measured with different structured assessment scales (Tricco et al., 2018).

Besides the treatment of cognitive impairment, antidementia drugs may have a favourable effect on neuropsychiatric symptoms, although several studies present differing results. For example, donepezil has shown its efficacy on depression, anxiety, irritability, apathy, delusions, hallucinations, disinhibition, and agitation in people with Alzheimer's dementia, and on delusions, hallucinations, apathy, cognitive fluctuations, and depression in people with dementia with Lewy bodies, both in randomized controlled trials and real-world settings (Cummings et al., 2016). However, a meta-analysis conducted in 2015 showed that only galantamine, and not donepezil, had a positive effect on neuropsychiatric symptoms, although cholinesterase inhibitors as a group overall seemed to improve neuropsychiatric symptoms (Wang et al., 2015). Memantine showed a favourable effect by decreasing the level of agitation and aggression in people with Alzheimer's dementia (Parsons et al., 2013), but a later meta-analysis did not show any significant effect of memantine on neuropsychiatric symptoms in people with Alzheimer's dementia (Wang et al., 2015). Despite differing results in the mentioned studies, a recent network meta-analysis compared efficacy and tolerability of both cholinesterase inhibitors and memantine, at different dosages, and showed that none of the drugs did improve neuropsychiatric symptoms in people with Alzheimer's dementia (Dou et al., 2018).

Antidementia drugs are usually considered safe and well tolerated. Cholinesterase inhibitors were, as an example, found to be the safest drugs with respect of risk of mortality and risk of falling (Watt et al., 2020). However, they still may cause gastrointestinal symptoms and headache (Tricco et al., 2018). Despite conflicting results, antidementia drugs have still been proposed in the algorithm steps to treat non-emergent neuropsychiatric symptoms, that is, neuropsychiatric symptoms that do not put the patient or his/her caregivers in imminent danger (Chen et al., 2021; Davies et al., 2018).

2.3.3.4 Sedatives and hypnotics

As sleeping disorders are common in people with dementia, physicians may be tempted to prescribe drugs with sedative effect. A recent systematic Cochrane review showed that melatonin does not seem to have a beneficial effect on sleeping disturbances in people with Alzheimer's dementia (McCleery & Sharpley, 2020). Despite their sedative effect, neither benzodiazepines nor hypnotics, such as zopiclone or zolpidem, are recommended in people with dementia (Norwegian Directorate of Health, 2017). Benzodiazepines cause sedation and respiratory depression, and combined with antipsychotics, which are also commonly used in the treatment of neuropsychiatric symptoms, seem to increase the mortality risk by more than 2-fold over a follow-up period of 180 days (Nørgaard et al., 2020). A systematic review of randomized controlled trials failed to show any efficacy of benzodiazepines in the treatment of neuropsychiatric symptoms (Tampi & Tampi, 2014). Benzodiazepines are

suggested as an emergent action to cause immediate sedation in extreme neuropsychiatric symptoms (Chen et al., 2021), but due to their wide range of side effects, they are generally still not recommended in the treatment of neuropsychiatric symptoms (Gerlach & Kales, 2020).

2.3.3.5 Non-psychotropic drugs

Antiepileptics have been studied in the treatment of neuropsychiatric symptoms, but neither valproate, carbamazepine, nor lamotrigine has shown favourable effects. Moreover, valproate and carbamazepine are associated with a wide range of toxic effects (McDermott & Gruenewald, 2019). On the other hand, gabapentin and pregabalin may have potential benefits in the treatment of aggression in dementia; however, most of the available studies are case reports and have small sample sizes (Supasitthumrong et al., 2019).

As neuropsychiatric symptoms may be caused by the lack of ability to express pain or discomfort, it has been proposed that analgesic and pain-management optimization always should be considered and may be effective in reducing neuropsychiatric symptoms (Chen et al., 2021; McDermott & Gruenewald, 2019). Even though analgesics are not psychotropic drugs, it is worth to mention that they are an important aspect of the pharmacological treatment of neuropsychiatric symptoms. A cluster randomized clinical trial, showed that following a stepwise approach with analgesic in nursing home residents with dementia, improved agitation, pain and overall neuropsychiatric symptoms (Husebø et al., 2011). Similarly, a recent review, presenting several studies about this subject, showed how analgesic treatment with paracetamol, or a stepwise treatment with paracetamol followed by morphine, buprenorphine, and pregabalin may be useful to reduce neuropsychiatric symptoms (Tampi et al., 2017).

2.3.3.6 Newer drugs

It is worth to mention that a completely new type of drugs, such as aducanumab and gantenerumab, has been given increased attention in the last years. They are a human monoclonal antibody that is selective to aggregates of beta amyloid in the brain, but have been showing differing clinical results on dementia-related symptoms (Aftab et al., 2021; Specialist Pharmacy Service, 2016).

Pimavanserin is a newer atypical antipsychotic drug that has been studied in the treatment of dementia-related psychosis. It differs from other antipsychotics because it has a low affinity to dopamine receptors, and it is already approved by the U.S. Food and Drug Administration (FDA) to treat Parkinson’s disease related psychosis. It has shown promising results in the

treatment of intense psychotic symptoms in people with Alzheimer's dementia (Ballard et al., 2019), but new studies are needed to support its efficacy results (Vinaşi et al., 2021).

Psychedelic drugs and cannabinoids have received a fair amount of attention in the past years, but there is no strong evidence that these drugs do have a favourable effect on either cognition or neuropsychiatric symptoms (Aftab et al., 2021).

2.3.4 Use of psychotropic drugs in nursing homes

In the past years, several studies have highlighted the widespread use of psychotropic drugs in patients living in long-term care facilities. The methodological differences between the studies make a precise comparison between the results, populations, and countries somewhat challenging, but the overall pattern indicates a high prevalence of psychotropic drugs prescriptions in nursing homes.

2.3.4.1 Psychotropic drugs prescription in Norway and worldwide

Several papers have focused on the prevalence of psychotropic drugs prescription in the general nursing home population in Europe, the US, and Australia. In Germany, for example, between 51.8% and 74.6% of nursing home residents received at least one psychotropic drug, and antipsychotics were the most frequent drugs prescribed (Richter et al., 2012). Similarly, a Dutch study showed that 56% of nursing home residents were prescribed at least one psychotropic drug, but in this study, the most frequent psychotropic drugs prescribed were antidepressants (29%), followed by antipsychotics (25%), anxiolytics (15%), and hypnotics (13%) (Smeets et al., 2017). Even in the US, antidepressants were the most common psychotropic drug prescribed (30-59%), followed by antipsychotics (19-28%), anxiolytics (12-23%), and sedatives/hypnotics (2-9%), and more than half of nursing home residents received at least one psychotropic drug (63-69%) (Galik & Resnick, 2013; Resnick et al., 2019). It is interesting to notice that the use of antipsychotics in the US is slowly decreasing: at the end of 2020, antipsychotics were in fact prescribed to 14.5% of nursing home patients (The U.S. Centers for Medicare & Medicaid Services, 2022). Different results were presented in a study from Australia, where under half of nursing home residents were prescribed one or more psychotropic drugs (48.1%); in this case antidepressants and antipsychotics were the most common psychotropic drugs prescribed (31.7% and 14.9%, respectively) (Brimelow et al., 2019).

This presented variation between countries and studies is pointed out in a literature review that summarized the prevalence of psychotropic drugs in Western European nursing homes. Among the 31 selected studies, the authors could only present comparable prevalence results for antipsychotic prescriptions, which ranged between 12% to 59% (pooled

percentage 27%) and for antidepressants prescriptions, which ranged from 19% to 68% (pooled percentage 40%) (Janus et al., 2016).

Other papers have focused on how psychotropic drugs were prescribed in nursing home patients with dementia. In the Netherlands, for example, 66% of the patients with dementia living in special care units received overall psychotropic drugs (antipsychotics, antidepressants, anxiolytics, and hypnotics), and antipsychotics were the most frequent psychotropic drug prescribed (Zuidema et al., 2011). However, differences between each special care unit were considerable for every single psychotropic drug category; as an example, antipsychotics were prescribed between 7% and 69% of the included participants (Zuidema et al., 2011). Similarly, in Switzerland, 70.8% nursing home residents with dementia received at least one psychotropic drug at nursing home admission; antipsychotics were also in this case the most frequent prescribed psychotropic drug (44.9% at baseline and 36.7% at 18 months follow-up) (Lustenberger et al., 2011). Even higher prevalence rates were found in nursing home patients with early onset dementia in the Netherlands: 81.3% were prescribed at least one psychotropic drug, where antipsychotics were the most frequently prescribed (50.7%), followed by antidepressants (49.3%), anxiolytics (30.7%), and hypnotics (17.8%) (Mulders et al., 2019).

When focusing on psychotropic polypharmacy in nursing home residents with dementia, it can be challenging to summarise results from different papers, as described in a recent meta-analysis. Among the 25 included papers from 17 different countries worldwide, the authors presented a high variability between the studies, but were still able to estimate that 33% of the residents received two or more psychotropic drugs, while 13.1% of the residents received three or more psychotropic drugs (Jester et al., 2021).

Some authors have also explored how the prescription of psychotropic drugs in nursing homes changed with time. In Australia, for instance, the pattern of psychotropic drugs prescriptions changed considerably during a time span of 16 years. In 1993, 58.9% of nursing home residents received at least one psychotropic drug, while 47.5% received at least one psychotropic drug in 2009; in addition, the prescription of hypnotics and anxiolytics decreased significantly, while the prescription of antidepressants increased from 15.6% in 1993 to 25.6% in 2009 (Snowdon et al., 2011). The total prevalence of antipsychotics prescription did not change in the same period, but there was a switch from using mostly first-generation antipsychotics to a more frequent prescription of second-generation antipsychotics (Snowdon et al., 2011). Similarly, six Norwegian nursing home cohorts were examined between 1997 and 2009. The overall psychotropic drugs prescription increased from 57.6% to 70.5% (Ruths et al., 2013). Specifically, the prescription prevalence of

anxiolytics increased significantly from 14.9% to 21.9%, as well as for hypnotics (from 14.5% to 22.9%) and antidepressants (from 31.5% to 50.9%) (Ruths et al., 2013). Another Norwegian study, on the other hand, presented a stable prevalence for most of the psychotropic drug categories between 2004 and 2011, except for antipsychotics, which prevalence decreased significantly between the two time points (from 24.1% to 16.7%) (Selbaek et al., 2017). In the same study, the prevalence of patients receiving at least one psychotropic drug was 72.9% in 2004-2005 and 68.9% in 2010-2011 (Selbaek et al., 2017). Another Norwegian study, following the same patient cohort over a 72-month period, found a high prescription rate for any psychotropic drug (72.9-63.3%), and a high persistence rate for any psychotropic drug category (except antidementia drugs) throughout all the study period (>50%) (Helvik et al., 2017). Finally, a Canadian cohort longitudinal study, followed nursing home patients with dementia from 2004 to 2013, and presented a large decrease in the prescription of benzodiazepines (11% point decrease) and atypical antipsychotics (4% point decrease), a large increase in the prescription of antidepressants (15% point increase for non-sedative antidepressants defined as SSRI and bupropion, and 9% point increase for sedative-antidepressants defined as TCA, mirtazapine and trazodone), and an increase in the amount of patients receiving at least one psychotropic drug (from 75% to 79%) (Vasudev et al., 2015).

2.3.4.2 Longitudinal studies presenting psychotropic drug prescriptions from nursing home admission

As presented until now in this chapter, there is an extensive amount of literature reporting a high prevalence rate of psychotropic drugs in nursing home residents. However, to the best of my knowledge, most studies have a cross-sectional nature, and few authors have examined the prescription of psychotropic drugs from nursing home admission and over time, trying to find possible clinical or environmental factors which can explain or predict the prescription of psychotropic drugs.

Nygaard and colleagues, found that the prescription of psychotropic drugs in people admitted to Norwegian nursing homes increased during the nursing home stay (Nygaard, 2001). The authors found that 15% of the residents were prescribed at least one psychotropic drug, 30% used a psychotropic drug during at least half of the nursing home stay, and three out of four residents were prescribed a psychotropic drug after nursing home admission (Nygaard, 2001).

Pottegård and colleagues, have presented the prevalence and incidence rates of sedating medication in people followed before and after nursing home admission (Pottegård et al., 2021). The authors presented data concerning benzodiazepines, the hypnotics zopiclone

and zolpidem, the atypical antidepressants mirtazapine and mianserin, the second-generation antipsychotic quetiapine, and the antihistamine promethazine and melatonin (Pottegård et al., 2021). The authors found an increase in the use of quetiapine, mianserin, and mirtazapine after nursing home admission. This study was a registry data analysis, and did not present any clinical measurements in the studied population (Pottegård et al., 2021).

O'Connor and colleagues, followed 166 residents newly admitted to a nursing home in Melbourne, and presented that already at admission, antidepressants and antipsychotics were prescribed in 29.5 % and 27.1 % of the residents, respectively (O'Connor et al., 2010). The authors did not collect any data concerning the residents' physical or mental health status, but they found that after admission, antidepressants were started in 6.0% and stopped in 0.6% of the residents, while antipsychotics were started in 5.4% and stopped in 4.8% of the residents (O'Connor et al., 2010).

Lustenberger and colleagues, examined the prescription rates in nursing home residents at admission and during a 18-month follow-up period, and found that the presence of behavioural disturbances at admission, defined as wandering, aggression, socially disruptive behavior, and resistance to care, predicted the prescription of antipsychotics during follow up (Lustenberger et al., 2011).

Foebel and colleagues, examined possible correlations between clinical and environmental factors in a large cohort of newly admitted nursing home residents with the new use of antipsychotics after admission and within 180 days. The authors found that both residents with cognitive impairment, dementia, behavioural symptoms, and delusions were more likely to be prescribed antipsychotics (Foebel et al., 2015).

Ivanova and colleagues, collected data of nursing home residents two months, one year and two years after nursing home admission, and the authors described correlations between the residents' physical and mental health with the use of benzodiazepines, antipsychotics, and antidepressants (Ivanova et al., 2018). The authors found greater prescription rates of antipsychotics in residents whose dependency shifted from low to high during the two years follow up, and in those residents who developed dementia in the same time frame (Ivanova et al., 2018).

Maclagan and colleagues presented the prevalence, incidence and discontinuation rates of antipsychotics and benzodiazepines in recently admitted nursing home residents with dementia and followed prescription changes during their first six months stay (Maclagan et al., 2020). The authors presented possible associations with demographic data, frailty, comorbidity, and aggressive behaviour prior to nursing home admission (Maclagan et al., 2020). Women were more likely to have a more prevalent and persistent use of

benzodiazepines compared to men. In addition, frail residents were more likely to be prescribed antipsychotics and benzodiazepines, while people with more aggressive behaviour were more likely to be prescribed antipsychotics, and less likely to have an antipsychotic drug being discontinued (Maclagan et al., 2020).

2.3.4.3 Factors associated with psychotropic drug prescriptions in nursing homes

What can explain the generally high prescription rates presented in several studies worldwide? Many authors have analysed possible factors associated with psychotropic drug prescription. These factors can be roughly divided into nursing home-related factors, and resident-related factors. There is a high variability in the conducted studies.

When speaking about resident-related factors, neuropsychiatric symptoms seem to be correlated to psychotropic drug prescriptions. In Dutch residents with early-onset dementia, verbal agitation was associated with a higher risk of antipsychotics prescription (Mulders et al., 2019). Similarly, in the US, nursing home residents with more severe agitation were more likely to receive antipsychotics, while antidepressants were more likely to be prescribed to residents with stronger depressive symptoms (Resnick et al., 2019). In the same way, permanent restlessness in German nursing home residents was positively associated with psychotropic drug prescription (Richter et al., 2012). In Norway, a higher score on the Neuropsychiatric Inventory Nursing Home Version (NPI-NH) was associated with multi-psychotropic drug use in nursing home residents, and dementia was associated with a higher risk of receiving several psychotropic drugs (Gulla et al., 2016). In an Australian study conducted in nursing homes, having dementia was associated with a higher risk of being prescribed antidepressants, benzodiazepines, and antipsychotics (Brimelow et al., 2019).

In people with dementia, psychotropic drug use might itself be a risk factor for dependency on long term care and further admission to a nursing home. A German study followed people aged 60 years or older who received a dementia diagnosis and were not exposed to antipsychotics prior to the diagnosis. People who were prescribed antipsychotics had about twice the risk of being dependant on long-term care, and they had between 1.4 and 1.7 the risk of being admitted to a nursing home (Nerius et al., 2018). However, these results were not adjusted for possible confounders by indication, a limitation pointed out by the authors of this study (Nerius et al., 2018)

Higher physical dependency might be both a risk factor for, and a consequence of, psychotropic drug prescriptions. In German nursing home, higher level of care dependency for the residents was positively associated with psychotropic drug prescription (Richter et al., 2012), and in the US, nursing home residents receiving psychotropic drugs had a significantly lower physical function and lower sense of balance compared to those who did

not receive psychotropic drugs (Galik & Resnick, 2013). Physical diseases might also play a role in the prescription of psychotropic drugs: in Norwegian nursing homes, for example, diabetes mellitus was negatively associated with receiving more psychotropic drugs, while angina pectoris was positively associated with receiving more psychotropic drugs (Gulla et al., 2016). Pain may also contribute in the decision making on whether a resident should receive psychotropic drugs: in the US, nursing home residents with more pain were less likely to be prescribed antidepressants (Resnick et al., 2019). It is important to notice that nursing home residents not receiving psychotropic drugs seem to have a higher Quality of Life (Galik & Resnick, 2013).

Quantitative studies may be limitative, and do not always catch the complex dynamics in a clinical setting, which is influenced by knowledge, culture, and beliefs. A qualitative analysis of interviews with physicians and nurses, presented the complexity in decision making on psychotropic drug prescriptions: health care personnel may in fact decide to continue a psychotropic therapy because a resident's neuropsychiatric symptoms are stable, or to prevent the escalation of neuropsychiatric symptoms in other residents (Smeets et al., 2014). Limiting factors in taking action for, or against, the prescription of psychotropic drugs, might be less-experience of physicians and a short employment span of nurses (Smeets et al., 2014). Physicians seem to believe that antipsychotics have a calming effect on the residents, and antipsychotics reduce the risk of harm and level of distress on nursing home staff (Janus et al., 2018). Physicians also reported that discontinuing antipsychotics was a difficult task to carry out (Janus et al., 2018), as it requires considerable resources for the alternative psychosocial approach, and increases the fear for the return or worsening of symptoms (Simmons et al., 2018). Family resistance against antipsychotic discontinuation is also a registered barrier (Simmons et al., 2018).

A recent scoping review analysed facilitators and barriers associated with the deprescribing of psychotropic drugs. Routines and systematic drug reviews may facilitate deprescribing; however, physicians reported that they had little time available to perform such reviews, and this was considered a barrier (Moth et al., 2021). Further, the lack of resources needed for non-pharmacological treatments, the lack of resources for educating family members, the lack of qualification to treat neuropsychiatric symptoms in dementia, and the lack of expertise to manage complex medication in dementia care, were all barriers to the modification of an established psychotropic drug therapy (Moth et al., 2021). Discontinuation of psychotropic drugs seems to be difficult to achieve when physicians and nurses share a high level of barriers and little willingness to discontinue a therapy (Azermai et al., 2014). When nursing home staff and physician are willing to cooperate, listening to each other's opinions, and

making a joint decision, deprescribing psychotropic drugs might be an easier task to carry out (Moth et al., 2021).

2.4 Polypharmacy in the geriatric patient

2.4.1 Definition of polypharmacy, risk factors, and consequences

A very general definition of polypharmacy is the use or prescription of many drugs, or the use of an excessive number of drugs at the same time (WHO Centre for Health Development, 2004). Traditionally, the term “polypharmacy” is used to refer to the prescription of five or more medications at the same time (World Health Organization, 2019). However, this definition is indeed reductive, as a recent systematic review showed. There were in fact 138 different definitions of polypharmacy ranging from numerical definitions to qualitative definitions, or a combination of these two definitions (Masnoon et al., 2017). Even though this systematic review showed that the majority of definitions were numerical, and half of them referred to polypharmacy as the concomitant use of five or more drugs (Masnoon et al., 2017), the heterogeneity of definitions in literature can be problematic and makes the evaluation of polypharmacy for a physician more challenging. Because polypharmacy may be necessary, and not necessarily harmful for a patient, descriptive definitions that focus on appropriateness, rather than the number of prescribed drugs, can be more helpful in a clinical setting to evaluate a patient’s medication. The World Health Organization has therefore defined polypharmacy as appropriate when a patient is prescribed the right amount of drugs with specific therapeutic goals, which are achieved or shall be achieved, with a minimal risk of adverse reactions and a good adherence from the patient (World Health Organization, 2019).

Despite the multitude of definitions of polypharmacy, and even if polypharmacy may be defined as appropriate, the use of multiple drugs at the same time is associated with hospitalization, falls, cognitive impairment (particularly for psychotropic and anticholinergic drugs), physical impairment, frailty, and mortality. However, a causal relationship with these factors is still unclear (Pazan & Wehling, 2021).

Even if polypharmacy may be considered appropriate after a careful clinical evaluation, it is still common to refer to polypharmacy as negative. Several predictors have been correlated to polypharmacy in the older patient, and many diseases seem to be associated with a higher risk of polypharmacy: cardiovascular disease, heart failure, and atrial fibrillation are examples (Nobili et al., 2011). In the US, predictors for polypharmacy (>12 drugs) were being female, being of African-American or Hispanic ethnicity, living in a micropolitan or rural area, and having a high prevalence of multimorbidity (Ellenbogen et al., 2020).

Older age and being woman are associated with a higher risk of polypharmacy, although for people above 70 years old, the gender difference levels out (Hovstadius & Petersson, 2012). Polypharmacy may also be caused by the patient's behaviour, such as the excessive self-medication with over-the-counter drugs, or by receiving medications from friends or relatives (Hovstadius & Petersson, 2012).

A physician's working environment has also been discussed as a possible risk factor for polypharmacy: excessive workload, lack of competence and lack of proper medication reviews, and the misinterpretation of adverse effects as new symptoms to be medicated may all be contributing factors (Hovstadius & Petersson, 2012).

Lastly, the strict adherence to disease-specific guidelines may also increase the risk of polypharmacy in older people, who suffer from multiple conditions, particularly when medication is prescribed on the long-term (Tinetti et al., 2004).

The management of polypharmacy is complex, and it requires taking into consideration both the patient's perspective and factors related to the healthcare system where a patient is treated. Thus, to succeed in reducing or preventing inappropriate polypharmacy, different actions are required on both the patient, by involving the person in the decision-making, and on the organizational culture, encouraging teamwork, innovation, and risk taking (Mair et al., 2017).

In Norway, nursing home residents in the period between 2009 and 2011 received a mean of 6.7 regular medications (Nyborg et al., 2017), and similar results were found in another Norwegian study which data were collected between 2011 and 2014 (mean of 6.8 ± 0.9 drugs) (Fog et al., 2020).

Polypharmacy is prevalent in residents living in long-term care facilities. A systematic review showed that between 38.1% and 91.2% of older residents living in long-term care facilities received five or more medications at the same time (Jokanovic et al., 2015). In the same systematic review, the authors found that the number of prescribers, recent hospital discharge, and comorbidity were associated to a higher risk of polypharmacy, while older age, longer stay in a facility, lower level of functioning, and cognitive impairment were associated to a lower risk of polypharmacy (Jokanovic et al., 2015).

Polypharmacy remains a complex problem to evaluate in older people with multimorbidity, and clinicians should carry out a comprehensive and dynamic assessment, with the purpose of a beneficial reduction in the amount of prescribed drugs (Hoel et al., 2021). The few guidelines that focus on the reduction of polypharmacy, and which are considered good, shift from a disease-oriented approach to a more practical approach that takes into consideration

the whole patient, and his or her ability of self-management. The guidelines provide detailed practical recommendations and algorithms, as well as supportive action tools in the decision-making process (Muth et al., 2019).

2.4.2 Potentially inappropriate medication, adverse drug events, and adverse drug reactions

When speaking of polypharmacy as a potentially harmful phenomenon for the older adults, there are some other terms, commonly used in the literature, that need to be elucidated.

Potentially inappropriate medication (PIM) is defined as a medication or a group of medications with an unfavourable balance between benefits and harms for a person (Steinman et al., 2015). However, this term refers to the potential harm and not to the actual harm. For some people, as an example, medications that are defined as potentially inappropriate on a general basis, are in fact appropriate (Steinman et al., 2015).

Studies that have reported PIM in older people show a wide prevalence range. For example, a systematic review of studies reporting PIM in people with dementia, showed that the prevalence of at least one PIM was between 14% and 74%, versus 11% to 44% in people without dementia (Hukins et al., 2019). The prevalence of PIMs in nursing homes seem to be generally high. In France, the prevalence of patients receiving at least one PIM was 77.4% (Qassemi et al., 2020), while in Belgium the prevalence was 64.1% (Fournier et al., 2020), and in Norway 57% of nursing home residents received at least one PIM, with a mean of 1.1 PIMs per resident (Halvorsen et al., 2019). The high prevalence of PIM is not necessarily connected to the fact that patients live in nursing homes. In fact, a study showed that almost half (44.3%) of the patients admitted to a nursing home were already using a PIM at admission (Maclagan et al., 2017). However, the same authors found an overall increase of patients receiving at least one PIM to 52.9% 180 days after admission, pointing out the joint responsibility of physicians treating patients in the community and physicians treating residents once they are admitted to a nursing home (Maclagan et al., 2017).

When referring to actual (and not potential) harmful effects of a medication, it is important to differentiate between the terms found in literature. The World Health Organization defines an Adverse Drug Reaction (ADR) as a “response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function” (WHO Meeting on International Drug Monitoring: the Role of National Centres (1971: Geneva, Switzerland) & World Health Organization, 1972). In the literature describing ADRs, other terms such as “adverse event”, “adverse reaction”, “adverse drug event” or “adverse effects” may be found and used interchangeably.

When a phenomenon related to a drug administration occurs unexpectedly, adverse effect and adverse reaction are synonym terms. The first refers to the drug's point of view, and the second refers to the patient's point of view (Aronson & Ferner, 2005). Even if one can find the term adverse event or adverse drug event referring to ADRs in the literature, this is not always correct. An adverse event is a more general term, referring to an adverse outcome that happens while a patient is being treated with a drug, but has not necessarily a causal relationship with the drug (Aronson & Ferner, 2005). In a more recent glossary, the World Health Organization has simplified the definitions combining the terms "adverse event" and "adverse reaction", and defining them as "any undesirable or unwanted consequence of a preventive, diagnostic, or therapeutic procedure" (WHO Centre for Health Development, 2004). Yet, this definition may still imply causality between a taken drug and an adverse event. Aronson has therefore proposed a new modified definition, which implicitly also includes medication errors as possible causes of ADRs: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product" (Aronson & Ferner, 2005). To be precise and consistent, in this thesis I will use the term Adverse Drug Reaction as stated in Aronson's definition.

ADRs can be dosage-related (i.e. toxic reactions, or allergic reactions at subtherapeutic dosages), time-related due to pharmacodynamic or pharmacokinetics changes, or caused by factors such as genetics, age, gender or diseases that may make a patient more susceptible to an ADR (i.e.: renal insufficiency while being treated with lithium) (Aronson & Ferner, 2005).

Older people are at a higher risk of ADRs compared to younger people, and this is such an important issue that some authors have proposed that ADRs and drug-related harm should be considered a geriatric syndrome (Stevenson et al., 2019; Zazzara et al., 2021). A geriatric syndrome can be defined as a complex syndrome highly prevalent in older (and /or frail) adults, with multiple causes, and related to multimorbidity, a poor outcome, and associated with other geriatric syndromes (Stevenson et al., 2019). This shows that managing an older person's medication is complex and needs a careful approach. As presented in chapter 2.3.2, psychotropic drugs are medications that needs particular scrutiny and regular evaluation, as they may be a possible cause of ADRs, and further, a possible cause of geriatric syndromes.

Some Norwegian studies have adopted a broader definition, using the term "drug related problems", to investigate drug-related situations that need monitoring. This classification includes problems related to the drug choice, the dose, side effects, interactions, drug administration, lack of or need for monitoring efficacy or toxicity, and lack of or need for better documentation about prescribing (Ruths et al., 2007). By using this definition, a study

among 41 Norwegian nursing homes revealed a high proportion of residents (84.1%) having “drug related problems”, 33.9% of which were cause by psychotropic drugs and analgesics (Fog et al., 2020). However, adverse drug reactions were only 5.7% of all drug-related problems, and mostly related to benzodiazepines and antipsychotics (Fog et al., 2020). The authors found a noticeable variation of the mean number of drug-related problems per resident between different nursing homes, ranging from 0.5 to 3.5 (Fog et al., 2020). Similarly, another Norwegian study found that nursing home residents had a mean of 3.7 drug related problems, and when these were made clear to the physicians, 71.8% of these problems were accepted and acted on (Devik et al., 2018).

Finally, a meta-analysis of 23 studies reported adverse outcomes related to the use of psychotropic drugs in nursing homes (adverse event, hospitalization, falls/fractures, and death) (Lapeyre-Mestre, 2016). Independently of the prescribed psychotropic drug, the prescription of higher doses, the recent treatment initiation, and the recent increase in doses, were all associated with a higher risk of adverse outcomes (Lapeyre-Mestre, 2016), making psychotropic drugs among the medications administered in nursing home residents that need extra careful and continuous evaluation.

2.4.3 Structured drug-chart reviews and their effectiveness

As presented in chapter 2.4.1, there are several tools and/or algorithms created to manage polypharmacy and evaluate the appropriateness of prescriptions. Drug-review lists approach the complexity of medication in people with polypharmacy, and they are helping tools for physicians to optimize their patients’ medication. These lists may take into consideration the individuality of a patient, whose medications need to be reviewed (disease-oriented lists), while other lists are merely descriptive and do not require the knowledge of a patient’s history to suggest drug modifications (drug-oriented lists) (Pazan et al., 2019). Another way of classifying these lists is whether they explicitly name medications or not (explicit lists / implicit lists). There is a high variation in how these lists have been created and structured, but generally speaking they consist of a combination of guidelines and opinions of experts on the matter.

To begin with, drug-review lists were created to uncover possible overtreatment in older patients, and they are referred to as negative lists, as they report medications that should be considered tapered or stopped. One of the earliest lists published was the Beers criteria list, developed to uncover inappropriate medications in people living in nursing homes (Beers et al., 1991). This list have been modified several times during the past years, and the American Geriatrics Society published its latest update in 2019 (American Geriatrics Society, 2019). In this last update, as an example, SNRIs have been added as medications to be

avoided in people with a history of falls and fractures, aripiprazole was removed as preferred antipsychotic agent to use in people with Parkinson's disease, and pimavanserin was added as a preferred agent for the same indication (American Geriatrics Society, 2019).

Other lists have been developed to address not only the problematic overtreatment with PIMs, but also the issues related to undertreatment in older patients. START/STOPP is an example of explicit list using this approach (Gallagher et al., 2008), and is considered a combined drug-oriented and disease-oriented explicit list, as it requires the knowledge of a patient's medical history to evaluate which criteria in the list are relevant. The START/STOPP list was latest updated in 2015 (O'Mahony et al., 2015). In this update, virtually all psychotropic drug categories are mentioned as potentially inappropriate in people aged 65 years or older; however, non-TCA antidepressants, SSRIs or SNRIs are still recommended in people with severe depression or anxiety, while antidementia drugs are recommended as stated in chapter 2.3.1 (O'Mahony et al., 2015). This list points out that there is no absolute right or wrong choice in the psychotropic drug management of older people, as physicians need to consider the individual situation for each patient.

In 2010, a panel of 38 German speaking experts developed the PRISCUS list, another explicit list of PIMs that should be prescribed with caution in older patients (Holt et al., 2010). According to this list, several TCA, the SSRI fluoxetine, the MAOI tranylcypromine (available in Norway as Compassionate-Use), and several sedatives and hypnotics among psychotropic drugs defined as PIMs. Interestingly, this list does not only present the reason why these drugs are considered PIM, but reports, for each drug, possible therapeutic alternatives and precautions to be taken in case the drug is considered useful in a particular patient (Holt et al., 2010). Not much differently, the result of an international European collaboration combining and evaluating criteria from the PRISCUS list, the Beers criteria, and two PIM lists developed in France and Canada, gave birth to the EU(7)-PIM list (Renom-Guiteras et al., 2015). In this list, all the psychotropic drug categories are represented and mentioned as PIMs (Renom-Guiteras et al., 2015). Similarly to START/STOPP, the EU(7)-PIM list reports considerations about each drug and the reasons why a drug is mentioned; in addition, the EU(7)-PIM list, just as the PRISCUS list, reports possible alternative therapies to the mentioned PIM, which may be an additional aid for a physician (Renom-Guiteras et al., 2015).

The Norwegian General Practice (NorGeP) criteria is another explicit list developed almost at the same time as START/STOPP in Norway (2009), and it reported PIMs in people aged 70 years or older. Because previous explicit lists, such as the original Beers criteria list, did not consider potentially harmful combinations of drugs, the NorGeP list addressed this issue

(Rognstad et al., 2009). However, it is important to mention that newer updates of the Beers Criteria and START/STOPP lists include the potential drug-drug interaction issues (American Geriatrics Society, 2019; O'Mahony et al., 2015). In 2015, a group of experts updated the NorGeP list making it clinically more relevant for residents living in nursing homes, and this gave birth to the Norwegian General Practice – Nursing Home (NorGep-NH) criteria (Nyborg et al., 2015). This list contains 34 criteria, divided in three subgroups: single substance criteria, combination criteria, and deprescribing criteria; the first two subgroups refers to substances or combinations of substances that should be avoided, the third subgroup refers to substances that should be evaluated carefully and rather deprescribed if possible (Nyborg et al., 2015). In the NorGeP-NH list, psychotropic drugs, such as benzodiazepines, hypnotics, antidepressants, antipsychotics, and antidementia drugs, are reported as potentially harmful medications or medications to be regularly assessed for prolonged use, either as single substances or in combination with other drugs (Nyborg et al., 2015).

Not all guidelines are explicit and structured as a list of specific drugs or drug categories to carefully assess. In 1992, Hanlon et al. developed an index called Medication Appropriateness Index (MAI) to score the appropriateness of a drug therapy (Hanlon et al., 1992). This differs from other explicit lists as MAI was built by evaluating 10 different criteria related to the use / prescription of one particular drug: indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and expenses (Hanlon et al., 1992). This is an example of implicit patient-oriented tool, but it has limitations: it requires time to be performed (about 10 minutes per drug), making this approach time consuming (Hanlon et al., 1992).

Another implicit tool is the Drug Burden Index, which shows a positive correlation between the number of anticholinergics and sedatives that are prescribed to an older person, and poorer physical mobility and cognitive function (Hilmer et al., 2007). This tool has possible positive implications if implemented in computerised decision support systems, but it is limited by the fact that the tool does not clearly define what anticholinergics and sedatives are, and does not consider the variable response of a drug in the older adult (Kouladjian et al., 2014) .

There are many similarities between the presented tools, but their ability of identifying PIMs may differ. A systematic review of 36 different PIM lists reported very little overlap between the lists (Motter et al., 2018). As an example, among 907 different classes of medications / medications reported altogether by the reviewed lists, only four drug classes and 44 medications were common among 69% of all the reviewed lists (Motter et al., 2018). Interestingly, benzodiazepines, TCA, first-generation antipsychotics, and the SSRI Fluoxetine

were among the most common medications reported across the reviewed 36 PIM lists (Motter et al., 2018). This review also pointed out that only few lists were developed for residents living in long-term care facilities. Among the 36 reviewed lists, only the Beers criteria, START/STOPP, and NorGeP-NH were pointed out as specific for nursing home residents, while most of the other lists were developed for general practice (Motter et al., 2018).

Another systematic review showed a wide variability in both the information included in implicit and explicit tools, and in their impact in a clinical setting. To begin with, only 26.2% of 42 tools reported a safer alternative medication suggestion, which may reduce the clinical applicability of a tool in daily practice (Masnoon et al., 2018). Further, out of the 42 reviewed tools, only 14 were investigated for associations with at least one patient-related outcome (hospitalization, mortality, falls, cognition decline, functional decline, adverse drug reactions, Quality of Life, discharged at home after hospitalization, and renal failure) (Masnoon et al., 2018). NorGeP-NH was included in this systematic review, but no reported studies analyzed the effect of NorGeP-NH on patient-related outcomes (Masnoon et al., 2018). Moreover, only MAI and START/STOPP reported a positive association between the specific tool and Quality of Life (Cahir et al., 2014; Masnoon et al., 2018; Olsson et al., 2011).

A recent Cochrane review evaluated the effectiveness of different tools to improve the appropriateness of polypharmacy in older people (Rankin et al., 2018). The authors focused on three main outcomes: improved medication appropriateness, reduced prescription of PIMs, and reduced prescribing omissions (Rankin et al., 2018). It is interesting to observe that the authors found no clear evidence that either implicit or explicit tools used in pharmaceutical care improved medication prescription in older patients (Rankin et al., 2018). Further, the authors argued that many factors might have a strong influence on the effectiveness of an intervention, and they name, as an example, the number of times an intervention is carried out, the amount of training health care personnel has, or how prescribers, nursing home staff, and patients are receptive to interventions and are willing to change a therapy (Rankin et al., 2018).

These reviews enlighten an important fact: there are no perfect tools that give a comprehensive evaluation of a person’s medication. Some authors call for a holistic tool that ideally provides both guidance in the evaluation of specific PIMs, and a scoring system indicating the total polypharmacy burden (Masnoon et al., 2018).

2.5 Interventions to reduce the use of psychotropic drugs in older people

In the previous chapter, I presented the different performance of implicit and explicit tools in identifying PIMs and which clinical implications these tools have on different outcomes. Speaking of psychotropic drugs as PIMs, are there interventions proven to be effective in reducing psychotropic medication?

A recent systematic review and meta-analysis reported the effect of focused psychotropic medication reviews on the optimization of psychotropic drug prescribing (Sheehan et al., 2018). Some reviewed studies supported the fact that focused psychotropic medication reviews were associated with either a reduction in doses / number of psychotropic drugs or a reduction in polypharmacy; other studies, however, did not support significant psychotropic drug changes, despite a multidisciplinary intervention (Sheehan et al., 2018). On a patient-level, this review reported studies showing a worsening in neuropsychiatric symptoms and Quality of Life after interventions were carried out, as well as studies which did not find any change in challenging behavior after an intervention program (Sheehan et al., 2018). The authors present a recurring problem. Few reviewed papers reported the use of validated instruments to examine clinical outcome variables, and most of the studies' medication reviews relied on the implicit evaluation of physicians (Sheehan et al., 2018).

A systematic review analyzed the effect of multidisciplinary psychosocial intervention, such as teaching, consultations, or cultural / process changes in nursing homes, on neuropsychiatric symptoms and on psychotropic drug prescription rates. Of three studies presenting outcomes on psychotropic drugs as a group, none showed a significant change (Birkenhäger-Gillesse et al., 2018). On studies reporting specific psychotropic drug categories, the authors found no decrease for antidepressants after interventions in five reviewed studies, while there was a significant decrease of antipsychotic prescription rates in the intervention groups of all nine reviewed studies (Birkenhäger-Gillesse et al., 2018). However, meta-analyses showed that short-term educational programs did not affect the prescription of psychotropic drugs, while interventions lasting longer, particularly when the interventions aimed to change the culture or processes in a nursing home, did indeed lower the prescription of psychotropic drugs (Birkenhäger-Gillesse et al., 2018).

In a systematic review of interventions that focused on the reduction of antipsychotics and / or benzodiazepines in nursing homes, educational interventions were the most common, followed by multicomponent interventions (mainly a combination of educational interventions and medication review) and psychiatric support (Hoyle et al., 2018). Six out of 11 different interventions led to a significant reduction in antipsychotic use, and only one study reported a significant reduction in benzodiazepine use after intervention (Hoyle et al., 2018). The

authors argued that it was difficult to interpret the results due to different measures utilization; moreover, clinical outcomes were very heterogeneous, and showed both worsening, stable and marginal improvement after interventions (Hoyle et al., 2018).

Another systematic review summarized interventions aimed at reducing inappropriate use of antipsychotics in people with dementia living in nursing homes. The most frequent interventions across the examined studies were educational, and despite the wide variation in interventions, the prescriptions of antipsychotics seemed to decrease in many of the reviewed studies (Thompson Coon et al., 2014). However, the authors still argued that the quality of the studies variated a lot, and many articles did not take into consideration other factors that may influence prescription rates, such as the level of staff training, or the belief of staff or family members about antipsychotic effects on a patient (Thompson Coon et al., 2014).

It seems important to include different health care providers in the evaluation of a patient's medication. A narrative review of three articles, described two studies of multidisciplinary interventions, conducted by nurses, occupational therapists or psychologists, and defined as a combination of medication reviews and training. The authors found an association between the interventions and the reduction of psychotropic drug prescriptions in people with dementia (McGrattan et al., 2017). A recent pilot study, showed that the collaboration of nursing home staff with a pharmacist, could help improving psychotropic drug medication in a skilled nursing facility, where 66% of the recommendations on medication changes were followed (Bell et al., 2020). However, involving external pharmacists may also not give the desired effect. As a qualitative study showed, when an intervention was led by third parties, such as community pharmacists, it did not seem to be successful. Either the pharmacists lacked training and professional confidence, or they had a challenging relationship with physicians, which consequently lead to a sense of inferiority (Maidment et al., 2016). A nursing home patient relates to different health care providers, and it seems crucial that their physicians are not left out in any multidisciplinary intervention. A systematic review, showed in fact that interdisciplinary interventions in nursing home care were positively associated with clinical outcomes, such as reduction in challenging behavior, depression, falls, pain, and psychotropic drugs, particularly when the primary care physicians were involved in the interventions (Nazir et al., 2013).

The inappropriate prescription of psychotropic drugs in nursing homes may be met with different approaches, and there might be upsides and downsides to any method among the presented interventions. Medication reviews may reduce psychotropic drug prescriptions in nursing home patients, but there is no strong data showing that this reduction is clinically

beneficial (Sheehan et al., 2018). However, there might be actual or estimated savings associated with medication reviews and/or educational interventions (Alldred et al., 2016; Sheehan et al., 2018). Multidisciplinary and multicomponent interventions can also reduce the number of inappropriate psychotropic drugs, but many interventions lack of individualization and do not take into consideration a patient's opinion and/or wishes concerning drug therapy (Sheehan et al., 2018).

The studies reported in the paragraph above do indeed show a high variability in interventions, outcome measures, and in which validated tools are used to measure these. This leads to different or contrasting results, which often seem difficult to interpret. Some authors have therefore called for a standardized core outcomes set (COS) in trials that aim for drug optimization in nursing home residents (Hoyle et al., 2018; Millar et al., 2017). The need for a minimum of COS for this scope, requires a complex selection process, using literature review and opinion collection from a multidisciplinary panel (Millar et al., 2017). Even though the development of a COS usually follows a standard procedure, it is still bound and limited by the opinion of the experts involved in the process. As an example, and to the best of my knowledge, the only COS developed for trials aimed to optimize medications in nursing homes had no psychiatrist involved in the process (Millar et al., 2017), despite the fact that psychotropic drugs are widely used in nursing homes. However, among 13 COS, the use of antipsychotics was the only drug-specific medication-related outcome (Millar et al., 2017).

2.6 Norwegian healthcare services and nursing homes

The Norwegian law for health care services (January 1st 2012), states that it is the duty of every Norwegian municipality to offer necessary health care services to all its citizens, included people with physical or psychiatric diseases, problems related to substance abuse, social problems, or any kind of disability (Helse- og omsorgstjenesteloven, 2012). Besides preventive health care measures, pregnancy and maternity care, emergency care, and psychosocial- and medical rehabilitation, every municipality is bound by law to offer home care assistance, personal assistance, institutional care, and Day Care Centers for people with dementia (Helse- og omsorgstjenesteloven, 2012). The Norwegian health care system follows the general principle in which a patient in need of a health care service will receive help at the lowest effective level (Haugan et al., 2016).

The services for older people are roughly divided in home care services and institutional care. Home care services consist of different services that do not require a patient to live in an institution. Table 2.6.1 summarizes the different types of home care services (Haugan et

al., 2016). In 2020, almost 200,000 patients received assistance at home, and the majority were under 80 years of age (Statistics Norway, 2021).

If a person needs practical or health services that cannot be delivered in a private home, he/she can apply to live in a care home. Care homes are generally apartments that are arranged in a way that facilitates the care service delivery. Often, these apartments are in the same building, have common areas to stimulate activities and social contact, and are connected to a nursing service. Patients who live in care homes and who need to be examined by a physician, usually relate to their own family physician.

Table 2.6.1 Different home care services in Norway, inspired by Haugan, Kjelvik et al. 2016.

Day Care Centers	Daytime centers for people with dementia. They offer different types of activities and increase social contact.
Security alarms	Alarms that people wear or have nearby and that are triggered when a person needs assistance.
Health services	Home nursing care. One or several nurses visit a patient in his / her own home once or several times a day.
	Physiotherapy or occupational therapy.
	Psychological support.
	Psychosocial support for people with substance abuse.
Practical help	Different type of help for practical needs.

In case patients need continuous health care, they can apply for admission to a nursing home. Nursing homes are institutions often divided in different units, always have available staff, and usually also have a physician connected to the facility at all times. In 2020, there were 39,241 nursing home beds in Norway, and the majority of patients living in these institutions were over 80 years old (26,951) (Statistics Norway, 2021). People living in care homes, on the other hand, amounted to 43,326, and about half were under 67 years of age. Even though the health care system ought to provide help at its lowest effective level, many patients still do not receive the appropriate care when needed. In august 2021, for example, 609 people in Norway were in need of a nursing home bed, but were still on a waiting list (Norwegian Directorate of Health, 2022).

Institutional care is divided in two categories: short-term units and long-term units. Short-term units offer beds to people who need a temporary institutional admission, either after hospital discharge, or for short-term observations, examinations, treatment, and rehabilitation. Once patients are discharged from a short-term unit, they usually continue living at home. However, it is not uncommon that people who are not able to live at home anymore, but who

are not yet offered a nursing home bed, stay in a short-term unit waiting for a long-term nursing home admission.

There is a large variety in the types of long-term nursing homes available in Norway, and they differ substantially among municipalities. An example of different unit types is presented in table 2.6.2. There is also a wide variability in the time physicians dedicate to each patient in a nursing home. It has been calculated that in 2014, every nursing home patient in Norway had about 30 minutes of physician-time available per week (Haugan et al., 2016).

Table 2.6.2 Examples of long-term nursing home units in Norway, inspired by the municipality of Oslo.

Ordinary units	Units generally dedicated to residents with somatic problems who need continuous health care service.
Special care units	Units with a higher staff : resident ratio, that variate in type and size. They are usually separated from the general nursing home population and are dedicated to people with dementia in need of extra care. Some units are also dedicated to people with dementia with severe neuropsychiatric symptoms. Some special care units are dedicated to people with young-onset dementia.
Special psychiatric units	Units with a higher staff : resident ratio, dedicated to people with severe psychiatric disease who need continuous and specialized care.
Other types	Units that are particularly dedicated to older residents with different diseases and/or disabilities, such as substance abuse, blindness, deafness, neurological disorders.

3.0 Thesis aim

The presented literature in the introduction, and in particular in chapter 2.3.4., shows a paucity and a wide variability in studies examining the course of psychotropic drugs prescriptions in nursing home patients from admission, and over time. Thus, the first aim of this thesis (substudy 1, paper 1 and 2) is to report a comprehensive examination of the course of psychotropic drug prescriptions from admission and over time, in Norwegian nursing homes. Further, we differentiated the prescriptions of psychotropic drug categories and reported which resident-related and nursing home-related factors were associated with psychotropic drug prescriptions.

The high prevalence of psychotropic drug prescriptions in nursing homes is not new knowledge, and psychotropic drugs are reported as PIMs in many explicit lists. However, as presented in chapter 2.5, multidisciplinary interventions aimed to reduce the use of psychotropic drugs in nursing homes, including the use of PIM lists, are difficult to interpret, but may reduce the number of psychotropic drugs when inappropriate. Yet, the beneficial effects of this reduction are not clear (Sheehan et al., 2018). In addition, as presented in chapter 2.4.3, few studies testing the effect of explicit PIM lists, focus on their clinical impact on the patients (Masnoon et al., 2018). The NorGeP-NH list has been developed in Norway as an explicit PIM list (Nyborg et al., 2015), but to the best of my knowledge, it has never been tested in a real-world setting to examine its effect on resident-related outcomes (Masnoon et al., 2018). Thus, the second aim of this thesis (substudy 2, paper 3), is to examine if the application of NorGeP-NH in a real-world practice, influenced the residents' Quality of Life, physical and mental health, and if it can reduce the prescription rates of psychotropic drugs in Norwegian nursing homes.

4.0 Materials and methods

4.1 Substudy 1 – The prescription of psychotropic drugs in Norwegian nursing homes from admission and over time

Substudy 1 refers to paper 1 and 2, were we used data that were collected during a previous study, the Resource Use and Disease Course in Dementia – Nursing Home (REDIC-NH) (Roen et al., 2017). Paper 1 and 2 are observational longitudinal cohort studies. Although details about REDIC-NH have been published in the previous cited paper, I will present a summary of the methods for data collection in the next chapter.

4.1.1 Data collection

The REDIC-NH study collected data from 47 Norwegian nursing homes located in four different Norwegian counties. The included participants were residents newly admitted to the nursing homes, aged 65 years or older, or younger than 65 years but with confirmed dementia. Residents were to be expected to live in the nursing home for at least four weeks. Residents were excluded if their life expectancy was less than six weeks.

Baseline data were collected between March 2012 and November 2014. Further, residents' data were collected every six months, through direct interviews with the residents, with their next of kin, and the nursing home personnel responsible for the residents' care. The main responsible for data collection were the healthcare personnel in the nursing homes, most of them were registered nurses (74%), and they were supervised by 10 research nurses. The responsible for data collection and the research nurses participated in a two-day and a five-day training program, respectively. Demographic data and data about the residents' medications were collected through documentation and / or the residents' journal records. Three physicians with a large experience in psychogeriatrics, reviewed the information collected for each patient, and set a dementia diagnosis according to the International Classification of Diseases, 10th Revision (ICD-10) criteria (World Health Organization, 1993), the Third report of the Dementia with Lewy bodies Consortium criteria (McKeith et al., 2005), a consensus on clinical diagnostic criteria for frontotemporal lobar degeneration (Neary et al., 1998), and criteria from the consensus of the International Working Group on Mild Cognitive Impairment (Winblad et al., 2004).

4.1.2 Assessments

In this chapter, I will describe the clinical and environmental information we used in paper 1 and 2, together with the assessment tools used to collect the data. Table 4.1.2.1 summarizes what is reported in the text below, and specifies which variables are used for paper 1 and 2.

4.1.2.1 Cognitive function and dementia severity

The Mini-mental State Examination (MMSE) was used to assess residents' cognitive function (Folstein et al., 1975). This is a cognitive test commonly used to screen residents' cognitive impairment. The MMSE has 20 standardized questions examining different aspect of a person's cognition: orientation to time and place, registration, attention and calculation, recall, language, repetition, and the ability to execute complex commands (Folstein et al., 1975). The total score is calculated by summing up the individual scores obtained for each question. The score ranges between 0 and 30, where higher scores indicate better cognitive function (Folstein et al., 1975).

Dementia severity was assessed with the Clinical Dementia Rating (CDR) scale (Morris, 1993). This is a proxy-based assessment tool scored by caregivers who have observed a resident for at least four weeks. The tool assesses six symptom dimensions related to dementia: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Each item can be scored from 0 to 3. The total score can be calculated in two ways: by summing up the individual score of each item (CDR sum of boxes (sob), ranging score 0-18) or by using a specific algorithm (CDR total score, ranging score 0-3) (Morris, 1993). In both cases, a higher score indicates a more severe degree of dementia.

4.1.2.2 Neuropsychiatric symptoms

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory 12-item nursing home version (NPI-NH) (Cummings et al., 1994). This is a proxy-based tool that assesses 12 different types of dementia-related neuropsychiatric symptoms that are observed during the four weeks prior the assessment: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behaviour, sleep/night-time behaviour disorders, and appetite and eating disorders (Cummings et al., 1994). Each item in the NPI-NH is scored for its presence/absence (yes/no), its severity (score 1-3), and its frequency (score 1-4). Subsequently, for each item, the severity score is multiplied by the frequency score, and the results are summed up (NPI total score, ranging score 0-144). The NPI-NH also collects data about the occupational disruptiveness for each item, with a ranging item score 0-5, and a ranging total score 0-60. Higher scores indicate higher degree of symptom severity. A Norwegian principal component analysis identified three subsyndromes, defined as agitation (sum of NPI scores for agitation/aggression, disinhibition, and irritability), psychosis (sum of NPI scores for delusions and hallucinations), and affective symptoms (sum of NPI scores for depression and anxiety) (Selbaek & Engedal, 2012).

Depression was assessed with the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), a proxy-based assessment tool evaluating several depression symptoms that can be found in people with dementia during the last week prior the assessment: mood-related signs, behavioural disturbances, physical signs, cyclic functions, and ideational disturbance. The scale has 19 different items, and each item can be scored from 0 to 2. The total score can range between 0 to 38, where a higher score indicates more severe depressive symptoms (Alexopoulos et al., 1988).

4.1.2.3 Physical health status and pain

The General Medical Health Rating (GMHR) scale was used to assess the general medical health status (Lyketsos et al., 1999). This tool uses a descriptive scoring system that takes into consideration the number of stable or unstable medical conditions, the number of daily prescriptions, and the clinical appearance. The attributed score can be excellent, good, fair, or poor (Lyketsos et al., 1999).

The Charlson Comorbidity Index was used to assess medical comorbidity (Charlson et al., 1987). This tool has 18 items grouping different disease categories. The total index score is calculated by using an algorithm which takes into consideration the severity of different diseases (Charlson et al., 1987). Higher scores indicate a higher level of comorbidity, severity of medical condition, and worse prognosis (Charlson et al., 1994).

Pain was assessed with the Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID-2), a proxy-based observational tool developed to assess pain in residents with severe cognitive impairment (Husebø et al., 2007). MOBID-2 has ten different items that take into consideration different parts of the body that may be painful, and expressions and behaviors that may be related to pain. Each item can be scored from 0 to 10. Based on all the observations and item scores, the respondent gives a final score for the total pain intensity, ranging from 0 to 10. A higher score indicates a higher level of pain (Husebø et al., 2007).

4.1.2.4 Functioning in daily living and Quality of Life

The Physical Self-Maintenance Scale (PSMS) was used to determine the level of functioning in daily living (Lawton & Brody, 1969). This is a proxy-based tool used to assess the self-maintaining activities in a resident the seven days prior to the assessment. It takes into consideration six dimensions of self-maintaining: the ability to use the toilet, feeding, dressing, grooming, physical ambulation, and bathing. The PSMS can be scored with two methods. The first method sums up the individual scores for each item (item score ranging from 1 to 5), where the total score can range from 6 to 30. In this case a higher score indicates a lower level of functioning. The second method follows the original scoring

algorithm by Lawton and Brody, where each item can be scored either 1, if a patient has no disability related to that item, or 0, if a patient shows any form of disability. The total score in this case ranges from 0 to 6, where 6 indicates the highest level of functioning (Lawton & Brody, 1969). We used the latter scoring algorithm.

Quality of Life was measured with the Quality of Life in Late-Stage Dementia (QUALID) scale (Weiner et al., 2000). This is a proxy-based tool that describes if a person smiles, seems sad, cries, has facial expressions of discomfort, appears physically uncomfortable, verbalises discomfort, is irritable or aggressive, enjoys eating, enjoys touching or being touched, enjoys interacting with others, and appears calm and comfortable. Every item can be scored from 1 to 5. Every item score is summed up, giving a total score ranging from 11 to 55. A higher score indicates a lower Quality of Life (Weiner et al., 2000).

4.1.2.5 Drug prescriptions

Medications where registered with their Anatomical Therapeutic Chemical (ATC) classification system. Only daily medications were registered, and no data about as-needed medication were collected. Originally, daily dosages were also registered, but the quality of data collection was too imprecise, so dosages were not included in the study. Particularly for psychotropic drugs, medications were categorized in antidepressants (N06A), antipsychotics (N05A, lithium was not included), anxiolytics (N05B), sedatives and hypnotics (N05C), and antidementia drugs (N06D).

4.1.2.6 Nursing home characteristics

Information about the type of unit was collected. A unit was defined as a separate independent area where the residents living in the unit shared a common living room, and were under the care of the same nursing home staff during daytime. Nursing home units were grouped as regular units, special care units, and respite and rehabilitation units. For each participant, information about the number of residents living in the unit where the participant received care, the number of staff members working dayshift per unit, and the number of hours a physician was present in the unit was collected.

Table 4.1.2.1. Schematic of the assessment tools used to collect data and used in analyses for paper 1 and 2.

Clinical feature and nursing home characteristics	Assessment tools	Paper 1	Paper 2	Comments
Cognitive function	Mini-mental State Examination (MMSE)	X	X	In paper 2, MMSE-scores are presented only for descriptive statistics at baseline, and not included in further analyses due to missing data.
	Clinical Dementia Rating (CDR) scale		X	
Neuropsychiatric symptoms	Neuropsychiatric Inventory 12-item nursing home version (NPI-NH)	X	X	Subsyndrome scores (affective, psychosis, agitation, and apathy) are used in the regression analyses.
	Cornell Scale for Depression in Dementia (CSDD).	X	X	In paper 1, CSDD scores are presented only for descriptive statistics, and not included in regression analysis due to high correlation with NPI-NH scores.
Medication	Anatomic Therapeutic Chemical (ATC) classification system	X	X	Total number of medications prescribed daily; Psychotropic drugs grouped as antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics, and antidementia drugs.
Physical health status	General Medical Health Rating (GMHR) scale	X	X	
	Charlson Comorbidity Index	X	X	
	Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID-2)	X	X	In paper 2, MOBID-II-scores are presented only for descriptive statistics at baseline, and not included in further analyses due to missing data.
Functioning in daily living and Quality of Life	Physical Self-Maintenance Scale (PSMS)	X	X	
	Quality of Life in Late-Stage Dementia scale (QUALID)	X	X	
Nursing home characteristics	Type of unit	X	X	In paper 2, types of units are dichotomized into special care units and others, due to the low number of cases and missing values.
	Number of residents per unit	X	X	In paper 1, the number of residents per unit is reported only in the descriptive statistics at baseline, and is not included in the regression analyses due to high correlation with the number of staff members per unit.
	Number of staff members per unit	X	X	In paper 2, the number of staff members per unit is reported only in the descriptive statistics at baseline, and is not included in the regression analyses due to high correlation with the number of residents per unit.
	Number of physician-hours per week per unit.		X	

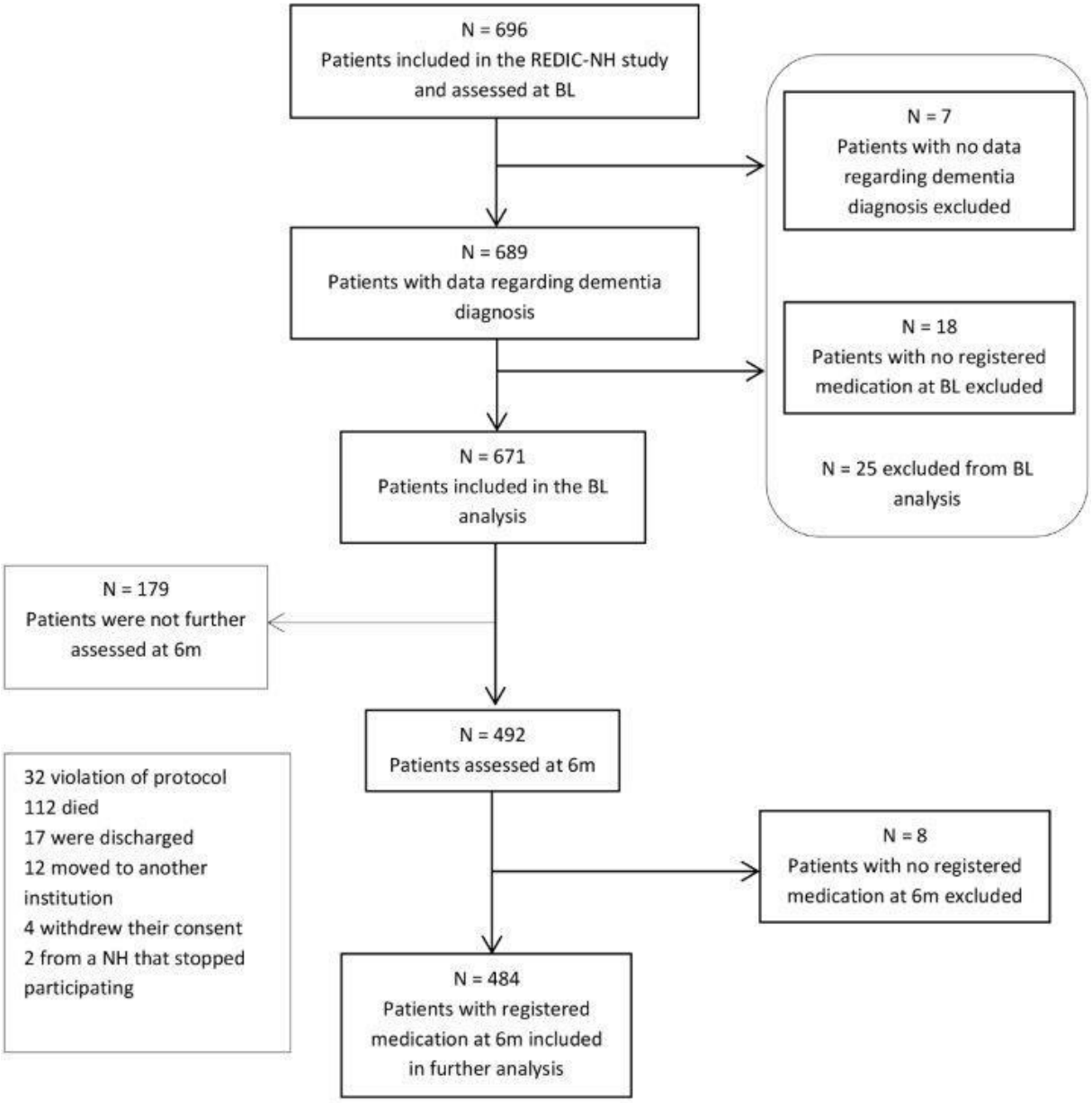
4.1.3 Participants and flow charts

As described in chapter 4.1.2, the substudy 1 used data from REDIC-NH (Roen et al., 2017). In total, 696 residents were included at baseline. The selection of participants for analysis, however, differed between paper 1 and 2.

In paper 1, where we focused on the prescription of psychotropic drugs during the first six months after nursing home admission, we excluded participants who had no data concerning dementia diagnosis, and who had no data concerning medication prescriptions at baseline (N= 25 participants excluded from baseline analyses). At 6-months follow-up, 492 persons were still participating to the study, and 179 were lost to follow-up due to either violation of protocol, death, discharge, movement to a different institution, consent withdrawal, or nursing home withdrawal from the study. Further, at six months follow-up, eight participants had no data concerning medication prescriptions and were excluded from analyses. Figure 4.1.1 shows the flowchart of paper 1.

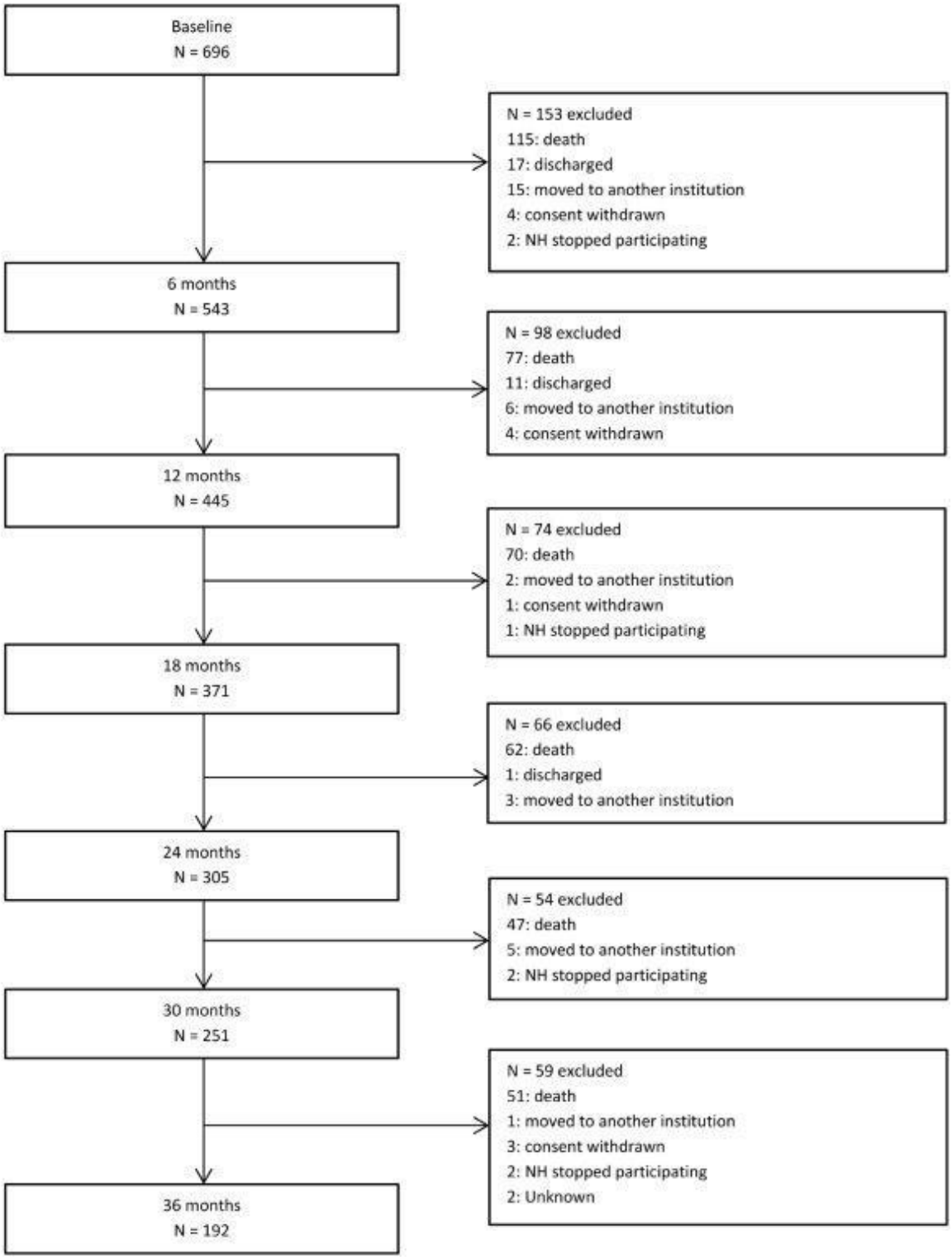
In paper 2, where we examined the change in prescription of psychotropic drugs from admission and over a 3-year period, we did not differentiate between people with or without dementia at admission, and we decided to include every participant with available data. This means that we included all the 696 participants at baseline, where 543 participants remained in the study at 6-months follow-up, 445 at 12-months follow-up, 371 at 18-months follow-up, 305 at 24-months follow-up, 251 at 30-months follow-up, and 192 at 36-months follow-up. Attrition causes between follow-up assessments are specified in Figure 4.1.2.

Figure 4.1.1. Flow chart of paper 1.



Legend: BL Baseline; 6m 6-months follow-up.

Figure 4.1.2. Flow chart of paper 2.



Legend: NH Nursing home.

4.1.4 Statistical analyses

4.1.4.1 Psychotropic drug prescriptions during the first 6 months from nursing home admission

In paper 1, we reported descriptive statistics as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. After presenting demographic and clinical characteristics of baseline data, we focused on analysing the prescriptions of psychotropic drugs in participants with dementia at baseline and at 6-months follow-up.

We reported data for the psychotropic drug categories antidepressants, antipsychotics, anxiolytics, hypnotics/sedatives, and antidementia drugs. For antipsychotics, we also presented data stratified by type (first- or second-generation antipsychotics). We presented the following:

1) prevalence data, defined as the proportion of participants prescribed a certain psychotropic drug category at baseline and 6-months follow-up;

2) incidence data, defined as the proportion of participants who were prescribed a psychotropic drug at 6-months follow-up divided by the proportion of pparticipants who were not prescribed the same psychotropic drug category at baseline;

3) persistence data, defined as the proportion of participants prescribed a psychotropic drug category at 6-months follow-up divided by the proportion of participants who were prescribed the same psychotropic drug category at baseline.

To assess differences at baseline between participants with and without dementia, as well as between participants included in the analyses and those who dropped out or were excluded from the analyses, we estimated a linear mixed model for continuous variables and a generalized linear mixed model for categorical variables. Both models contained random effect for unit nested within a nursing home.

To analyse changes in psychotropic drug prescriptions from baseline to 6-months follow-up, in relation to clinical and nursing home characteristics at baseline, we estimated a generalized linear model. This model had fixed effect for time dummy, with baseline as a reference, and for dementia status at baseline, with dementia as a reference, and the interaction between these two variables. The model had random intercepts for participants nested within nursing home units. Further, several clinical variables, as well as nursing home-related variables were included in the model as fixed effects, as well as the interaction between each variable and dementia status at baseline. Finally, we applied Akaike Information Criterion to minimize excessive interactions and variables in the model.

Because several variables had missing values, imputation was performed for those variables with less than 50% missing values. We estimated the regression models for those cases with no missing values on each variable. Included cases in the model were compared with excluded cases by linear mixed model for continuous variables, and generalized linear mixed model for categorical variables. Both models contained random effect for unit nested within nursing homes. We presented the results of this model as odds ratios with corresponding 95% confidence interval and a 5% significance level.

4.1.4.2 Psychotropic drug prescriptions during a 3-year follow up from nursing home admission

In paper 2, similarly as for paper 1, we reported clinical and nursing home-related characteristics at baseline, stratified by dementia diagnosis. We then presented prevalence data, as defined for paper 1, for the prescription of the same psychotropic drug categories as paper 1, but in this case for baseline, 6-, 12-, 18-, 24-, 30-, and 36-months follow-up. Then, we presented incidence data (as defined for paper 1) for two subsequent assessment points.

Instead of persistence data, we presented deprescribing data, defined as the proportion of participants not being prescribed a psychotropic drug category at one assessment point, divided by the proportion of participants being prescribed the same psychotropic drug category at the previous assessment point. In paper 2, we presented, as in paper 1, specific data for first- and second-generation antipsychotics, and we also specified, among antidementia drugs, data for cholinesterase inhibitors.

Further, we analysed whether predefined demographic, clinical and nursing home-related variables were associated with a change in time in odds of prescribing a particular psychotropic drug category. To do so, we estimated generalized linear mixed models, containing random effects for participants nested within a nursing home. First, we estimated an unadjusted model with second-order time component to examine if there was a non-linear trend in odds of prescribing psychotropic drugs. Further, we introduced each predefined variable, one at a time, in the model, as fixed effect together with its interaction with time. In the end, we estimated an adjusted model with all the included variables and interactions. In this case, to minimize excessive interactions, we applied Bayesian Information criterion.

Graphical representation of the unadjusted time trend was presented for each psychotropic drug category, at each assessment point, as odds of being prescribed a psychotropic drug, with their corresponding 95% confidence interval.

The results showing associations between a variable and the prescription of psychotropic drugs were presented as odds ratios with their correspondent 95% confidence interval, in case no interaction was present, or as regression coefficients and standard errors in

presence of interactions. In case of interactions, we also presented the results graphically. The level of significance was set at 5%.

Also in this paper, when cases had fewer than 50% missing values for particulate variables (CDR, CSDD, PSMS, QUALID, and NPI-NH scores), imputation was performed.

4.2 Substudy 2 – The effect of applying NorGeP-NH on nursing home residents' Quality of Life, mental and physical health, and psychotropic drugs prescriptions

The substudy 2 was a cluster randomized controlled trial conducted in Østfold County, Norway. Before inclusion, we contacted the healthcare administration in all the 19 municipalities distributed in the area served by the regional Østfold hospital. In total, 34 nursing homes were under the administration of these 19 municipalities, and they were invited to participate to the study. The administrative personnel received written information about the project, and they were offered an information meeting if they required that. Of the 34 potential nursing homes, 15 nursing homes agreed to participate to the study, and were involved in the following process. One nursing home, which agreed to participate, withdrew from the trial due to lack of resources, while patients were being assessed for eligibility. Figure 4.2.1 presents in detail the flowchart of the trial, described in detail in chapter 5.2.1.

4.2.1 Participants

All the residents living in the nursing home units that accepted to participate to the study were assessed for eligibility. The criteria for inclusion were as follows:

1) the participant was a nursing home resident;
2) the participant was expected to live for at least 12 weeks.

Exclusion criteria were as follows:

1) the resident had a terminal disease;
2) the resident had a severe somatic of psychiatric disease that caused too great debilitation, difficulties in cooperation, and/or where the assessments in this study were going to cause a too great physical or psychological burden;
3) the nursing home physician performed a structured drug chart review in the previous three months before inclusion.

Decision about eligibility was for the nursing home physician and nursing home personnel to make, as they knew each resident best. Eligibility criteria were thoroughly controlled prior to inclusion, making sure the study protocol was followed.

Figure 4.2.1 Flowchart of the trial.

Legend: NH Nursing home.

4.2.2 Lectures and assessments prior to randomization

After inclusion, but prior to randomization, the healthcare personnel in every included nursing home participated in a three-hour lecture about dementia and old age psychiatry. The following subjects were included in the lecture:

- Dementia, causes, prognosis, and treatment;
- Behavioural and psychological symptoms in dementia;
- Delirium;
- Depression and anxiety in old people;
- Psychosis in old people.

Selected personnel were chosen to be responsible for assessing the included participants with specific tools. To ensure that the tools were used properly, the chosen personnel participated in a three-hour seminar, and learned how to perform the predefined assessments.

Further, the personnel began to assess the included patients in the study. To make it practical, we accepted that the baseline assessments were collected during a one-week period.

The following information was collected at baseline:

Demographics

We collected data about year of birth, gender, years of education, and marital status.

Nursing home characteristics

We collected data about the type of nursing home unit, the number of residents living in the unit where the included participant lived, the number of caregivers working daytime shift during a weekday, and the number of hours a physician was available in the unit per week.

General clinical information

We asked the data collectors to register relevant diagnosis (if known), and information about the participant's sight and hearing.

Medication

Medication data were collected with the name, daily dosage, and the medication's Anatomical Therapeutic Chemical (ATC) classification system. It was also possible to specify whether a patient did not use any regular daily medication. We also collected data about the number of pro re nata (PRN) drugs.

Cognitive function and dementia severity

To assess cognitive function, we used the Montreal Cognitive Assessment (MoCA), a

cognitive test that examines eight cognitive domains: visuospatial / executive abilities, naming, memory, attention, language, abstraction, delayed recall, and orientation (Nasreddine et al., 2005). The total score is obtained by summing up the single scores for each item / task. The total score ranges between 0 and 30, where a higher score indicates a better cognitive function (Nasreddine et al., 2005).

Dementia severity was assessed with the Clinical Dementia Rating (CDR) scale (Morris, 1993). Details about this tool are reported in chapter 4.1.2.

Neuropsychiatric symptoms

A comprehensive evaluation of neuropsychiatric symptoms was assessed with the Neuropsychiatric Inventory 12-item nursing home version (NPI-NH) (Cummings et al., 1994). Depression was assessed with the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), and with the Montgomery And Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979). NPI-NH and CSDD are described in detail in chapter 4.1.2. MADRS is a clinical interview that assesses ten different items / symptom-dimensions related to depression: apparent and reported sadness, inner tension, reduced sleep and appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts (Montgomery & Åsberg, 1979). Each item is scored according to what the resident reports and what the clinician observes during the interview. Each item can be scored from 0 to 6, and the total score is obtained by summing up the item-scores. The total score can range from 0 to 60, where a higher score indicates a more severe depression (Montgomery & Åsberg, 1979). Anxiety was assessed with the Geriatric Anxiety Inventory (GAI) (Pachana et al., 2007), a 20-item questionnaire (yes /no) that can be filled either out by the resident, or that can be administered by a healthcare personnel. The total score is obtained by summing up the number of positive answers, and a higher total score indicates a higher level of anxiety (Pachana et al., 2007).

Activity of daily living, comorbidity and physical function

The Physical Self-Maintenance Scale (PSMS) was used to determine the level of functioning in daily living (Lawton & Brody, 1969). The level of medical comorbidity was assessed with the Charlson Comorbidity Index (Charlson et al., 1987), and the general medical health status was assessed with The General Medical Health Rating (GMHR) scale (Lyketsos et al., 1999). These three tools are described in detail in chapter 4.1.2.

The “Timed Up & Go” (TUG) test was used to measure the physical mobility (Podsiadlo & Richardson, 1991). This test consists of measuring the time it takes for a participant to stand up from a sitting position on a chair, walking straight three meters, turning around, walking back to the chair, and sitting down (Podsiadlo & Richardson, 1991).

Quality of Life

The Quality of Life was assessed with the Quality of Life in Late-Stage Dementia (QUALID) scale (Weiner et al., 2000), described in chapter 4.1.2.

4.2.3 Randomization

To begin with, every nursing home that accepted to participate to the study, was asked to provide the number of residents they were able to include and follow up. An independent statistician then performed a stratified randomization, by using a computer-generated algorithm, stratifying the nursing homes into four groups according to how many residents could be included from each nursing home, and then allocated the participating nursing homes into two arms. The results of the allocation were kept hidden from the participating nursing homes. Eligibility was then assessed by the nursing home physician responsible for the participating nursing home, but E.C. performed an independent examination of each eligible resident to confirm inclusion criteria and assess the capacity to consent. The capacity to consent was performed by a clinical interview, assessing a resident's ability to understand the given information, to recognize the information received in relation to the resident's situation, to reason about the presented information, and to express a concrete choice.

In case a nursing home had more eligible residents than the number of residents they could assess and follow up during the study, participants were selected by drawing lots.

Randomization of the two arms, into control nursing home and intervention nursing home, was performed by a random number generator, and its result was kept hidden from the nursing home until after baseline assessments were completed.

4.2.4 Intervention

The intervention was performed and completed within 2 - 2,5 weeks after the baseline assessments were completed, and consisted of an educational intervention first, and a drug chart review of the participant's medications thereafter.

The intervention included the following steps:

1) The nursing home physicians working in the intervention nursing homes attended a three-hour lecture, which included these subjects:
    - principles of pharmacology in older people;
    - the use of psychotropic drugs in older people;
    - how to conduct a drug chart review with the Norwegian General Practice – Nursing Home (NorGeP–NH) criteria (Nyborg et al., 2015).

    E.C. conducted this lecture face-to-face, it included the use of an electronic presentation as supportive material, and it was held in the nursing homes where the

physicians worked, after baseline data were collected. The physicians who attended the lecture received a copy of the electronic presentation after the lecture, and laminated NorGeP–NH list to use in the next step.

2) Within a two-week period after the lecture, physicians in the intervention nursing homes performed a drug chart review, following guidelines stated in NorGeP–NH. Physicians could consult E.C. (psychiatrist) if they needed to discuss prescription choices made during a review. However, the final decision about medication changes was the physician's responsibility.

4.2.5 Control group and follow-up assessments

The physicians treating the included residents in the control nursing homes were asked to follow up the residents as usual. All the participants were assessed eight and 12 weeks after baseline assessments, with the assessments described in chapter 4.2.2, except for data on demographics and nursing home characteristics, which were collected only at baseline. Once the study was terminated, the physicians working in the control nursing homes participated in the same seminar on psychopharmacology and NorGep-NH as described in chapter 4.2.4.

4.2.5 Outcomes

As the primary outcome of this study, we chose the difference in change in Quality of Life, measured with QUALID (Weiner et al., 2000), between the intervention nursing homes and control nursing homes. As secondary outcomes, we chose the difference in change from baseline to eight and 12 weeks, between intervention nursing homes and control nursing homes, in the following:

- total amount of prescribed drugs (regular and as needed);
- psychotropic drugs categories (antidepressants, antipsychotics, anxiolytics, hypnotic/sedatives, and antidementia drugs);
- depression assessed with CSDD and MADRS (Alexopoulos et al., 1988; Montgomery & Åsberg, 1979);
- neuropsychiatric symptoms measured with the NPI-NH total score and its affective-, psychosis-, and agitation subsyndrome scores (Cummings et al., 1994; Selbaek & Engedal, 2012);
- the level of cognitive impairment and dementia measured with MoCa and CDR (Morris, 1993; Nasreddine et al., 2005);
- the level of functioning in daily living assessed with PSMS (Lawton & Brody, 1969);
- the medical health, level of comorbidity and physical function assessed with GMHR, Charlson Comorbidity Index, and TUG (Charlson et al., 1987; Lyketsos et al., 1999; Podsiadlo & Richardson, 1991).

4.2.6 Power calculation

To calculate the number of participants to be included in this study, we considered a previous Norwegian paper, showing that residents newly admitted to Norwegian nursing homes had a mean (SD) QUALID score of 20 (7.2) (Roen et al., 2017). At the designing stage of this study, and to the best of our knowledge, we did not find previous RCTs where QUALID score was used as a primary outcome. Prior to power calculations, we therefore chose to define a change from baseline to 12-week follow-up in QUALID score of 33% as clinically important, to be sure that any changes caused by our intervention were clinically relevant. Assuming a SD of 7.2 in both intervention and control group, with a power of 80% and a level of significance set at 0.05, we calculated that we needed 39 participants in each group to be able to detect a 33% difference in change in QUALID score between intervention nursing homes and control nursing homes, from baseline to 12-weeks follow-up. We then considered the possible dropouts due to death. A Norwegian paper showed that in Norwegian nursing homes, about 25% of residents died within a year from nursing home admission (Sandvik et al., 2016). Because of that, we estimated that about 6-7% of participants would die during a period of 12 weeks, and we rounded up this to a 10% possible dropout. This led to an estimated number of 43 participants that needed to be included in each group. To begin with, we did not know how many nursing homes would participate to the study, and we assumed that about 10 nursing homes would respond positively. Considering a cluster effect on a nursing home level of 5%, we calculated that we needed about 60 participants in each group. Finally, we rounded up this estimation to 100 participants for each group.

4.2.7 Statistical analyses

4.2.7.1 Descriptive statistics

Baseline characteristics of each group were presented as follows:

- demographics;
- nursing home characteristics;
- clinical assessment scores;
- number of daily medications taken regularly;
- number of PRN drugs;
- number of patients exposed to a particular psychotropic drug category (antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics, and antidementia drugs) at each assessment point.

For continuous variables, we presented the results as means and standard deviations. For categorical variables, we presented results as frequencies and percentages.

4.2.7.2 Regression analyses

We assessed the difference in change in primary and secondary outcomes between intervention nursing homes and control nursing homes with the following methods:

- we estimated linear mixed models with fixed effect for time, allocation group, and the interaction between these two for continuous outcomes;

- we estimated generalized linear mixed models with fixed effect for time, allocation group, and interaction between these two for categorical outcomes.

For these analyses, we included cases with no missing data at baseline. According to the intra-class correlation coefficient, the cluster effect at nursing home level was non-negligible. Thus, all the models included random effects for nursing homes to adjust the results for cluster effects at nursing home level.

4.3 Ethics approval and considerations

The REDIC-NH study (Roen et al., 2017), which Substudy 1 (paper 1 and 2) is based on, was originally approved by the Regional Committee for Medical and Health Research Ethics (REK South-East A, 1738/2011). Through an amendment, the same Committee approved the use of data collected during the REDIC-NH study for Substudy 1, with the same reference number. The REDIC-NH study was registered on Clinicaltrials.gov (Identifier: NCT01920100).

The Substudy 2 was approved by the Regional Committee for Medical and Health Research Ethics (REK South-West D, 2017/2171). The Substudy 2 was registered on Clinicaltrials.gov (Identifier: NCT03736577).

Both substudies were based on the participants' written informed consent. The capacity to consent was evaluated by the nursing home personnel, who had a deeper knowledge of each participant. In both substudies, when a nursing home resident lacked the capacity to consent, a written informed consent was obtained by a participant's next of kin.

In the application and approval process, several ethical issues were considered and discussed. To begin with, we discussed the possible ethical issues related to the inclusion of residents with a reduced capacity to consent. Generally speaking, the participation to a study should rely to a participant's consent. However, if this criterion were strictly applied, people with cognitive impairment, and in particular with severe dementia, who did not understand the meaning of a research project, or were not able to give an informed consent, may be excluded from important studies. The nursing home population is heterogeneous, most

people living in nursing homes have dementia, and it is important that both observational and intervention studies are conducted in this population to both understand factors related to nursing home residents disease, and optimize interventions that increase their Quality of Life and the level of care. For the REDIC-NH study and the RCT, we argued that observations conducted to examine the residents' clinical characteristics are similar, if not alike, observations / assessments conducted during a normal clinical routine. This means that there would be no extra burden for the residents due to the assessments. We also argued that frequent assessment may lead to better observations and higher level of care. We explicitly argued that in case a resident actively showed resistance (either physical or verbal) to the assessment, they should not be included in the study. We also argued that a direct contact with a resident's next of kin would provide reliable feedback on whether or not a resident would have wanted to participate to the project if he/she could express their will.

Secondly, we discussed how the intervention would affect residents with reduced capacity to consent. Besides the frequent observations / assessments, discussed in the previous paragraph, medication changes may lead to discomfort, or reactivation of symptoms. However, medication changes would be performed after a thorough evaluation of the attending nursing home physician, and highly controlled by the nursing home staff. Any sign of discomfort would lead to a re-introduction of the previous drug / dosages, or the tapering / discontinuation of newly prescribed drugs, minimizing the negative effects. The alternative, not doing a review and medications changes because a person is not able to consent or express their opinion, would also be highly unethical and against good clinical practice. Further, we argued that the involvement of a resident's next of kin would be highly important to evaluate the effect / consequences of any medication change.

Thirdly, we were made aware of an ethical issue regarding the implementation of an intervention that focused on increasing knowledge in nursing home physicians. The regional ethical committee pointed out that it would be unethical to expose only the NH physicians working in the intervention nursing homes to an educational intervention, increasing their level of training compared to physicians working in the control nursing homes. Therefore, at the end of the study period, all nursing home physicians working in the control nursing homes received the same lecture on pharmacology, psychopharmacology, and use of NorGeP-NH that was held for the physicians working in the intervention nursing homes. This would give the residents of the control nursing homes the same benefits deriving from increased knowledge and level of training of their attending physicians.

5.0 Results from the three papers

5.1 Psychotropic drug prescriptions from nursing home admission and over time

5.1.1 Main results from paper 1

5.1.1.1 Sample characteristics at nursing home admission

The mean (SD) age of the included participants (N = 671) was 84.4 (7.5) years. Most participants were women (64.4%) and had dementia (83.9%). Compared with participants without dementia, residents with dementia had a statistically significant younger age (p = 0.021), had a lower score on the Charlson comorbidity index (p = 0.01), a lower score on MOBID 2 (pain) (p <0.001), a higher score for NPI-total score (p = 0.001), and a higher score for NPI-agitation and NPI-psychosis subsyndrome (p = 0.002 and p = 0.014 respectively). Residents with- and without dementia had comparable general medical health, assessed with GMHR.

5.1.1.2 Characteristics of the participants excluded from analyses and participants who dropped out

Compared to the participants included in the analyses, the residents who were excluded or who dropped out between the baseline data collection and the 6-months follow-up, had a poorer general medical health state assessed with GMHR (p = 0.002), a higher medical comorbidity assessed with the Charlson comorbidity index (p = 0.002), a lower level of functioning assessed with PSMS (p < 0.001), a higher level of depression assessed with CSDD (p = 0.036) and a lower Quality of Life assessed with QUALID (p = 0.010).

5.1.1.3 Medication prescriptions

At admission, participants were prescribed on average (SD) 6.1 (3.1) drugs. We found a statistically significant difference in the average number of daily prescribed drugs (p < 0.001) between people with dementia (mean 5.9 (SD 3.0)) and people without dementia (mean 7.5 (SD 3.5)). We found a significant increase (p = 0.008) in the number of people prescribed at least one psychotropic drug between baseline (67.5%) and 6-months follow-up (74.0%). Between baseline and 6-months follow-up we also found a statistically significant increase in the prescription rates of antidepressants (from 31.0% to 40.1%, p < 0.001), antipsychotics (from 13.5% to 19%, p < 0.001), anxiolytics (from 17.1% to 21.4%, p = 0.004), and sedatives/hypnotics (from 22.6% to 30.3%, p < 0.001). Typical antipsychotics had the lowest persistence rate (41.7%), but together with atypical antipsychotics, the persistence rate was 69.6%. Among all psychotropic drugs, antidepressants had the highest persistence rate (86%). The lowest incidence rate was for typical antipsychotics (2.6%), but together with

atypical antipsychotics, the incidence rate was 11.1%. Antidepressants had the highest incidence rate (19.5%).

5.1.1.4 Regression analyses: changes in prescriptions between baseline and 6-months follow-up, for psychotropic drug categories

The following results focus on the multiple regression models. Compared to the included cases (N = 402) in the regression analyses, the excluded cases (N = 82) had a significant lower level of functioning ($p = 0.004$), a higher NPI-total score ($p = 0.009$) and NPI-agitation subsyndrome score ($p = 0.013$), a lower Quality of Life assessed with QUALID ($p = 0.005$), lived more often in special care units ($p = 0.001$) and in units with a lower number of residents ($p = 0.001$).

Patients with younger age and higher NPI-affective subsyndrome score had higher odds of being prescribed antidepressants (OR 1.4; 95% CI 1.2-1.7; $p < 0.001$). We found that men with dementia had higher odds of receiving antidepressants compared to men without dementia, both at baseline ($p = 0.016$) and at 6-months follow-up ($p = 0.023$). We found a significant difference, between people with- and without dementia, in the association between NPI-psychosis subsyndrome scores and prescription of antidepressants ($p = 0.048$ for interaction). Further, for increasing Charlson comorbidity index (for values ≥ 2), participants with dementia were prescribed fewer antidepressants compared to people without dementia.

We could not estimate a multiple regression model for antipsychotics, due to their low prevalence rate.

For anxiolytics, we found no significant associations.

For sedatives and hypnotics, we found that prescription rates were positively associated with higher NPI-affective subsyndrome scores (OR 1.2; 95% CI 1.1-1.5, $p = 0.013$). We found a significant difference, between people with- and without dementia, in the prescription of sedatives and hypnotics for NPI-agitation subsyndrome scores < 5 at baseline, and for NPI-agitation subsyndrome scores < 4 at 6-months follow-up.

5.1.2 Main results from paper 2

5.1.2.1. Sample characteristics at nursing home admission

At admission (N = 696), most residents had dementia (83.8%), were female (64.1%), had a fair/poor general medical health state assessed with the GHMR (52.4%), and lived in regular units (55.3%). Compared with people without dementia, residents with dementia were on average (SD) 2.4 years younger (84.0 (7.5) years old for participants with dementia, 86.4 (7.0) years old for participants without dementia), had a slightly lower Charlson comorbidity

index (2.8 (2.1) for participants with dementia, 3.5 (2.8) for participants without dementia), lower MMSE score (14.8 (5.5) for participants with dementia, (22.5 (5.6) for participants without dementia), yet comparable level of functioning assessed with PSMS (1.5 (1.3) for both groups). Compared with residents without dementia, people with dementia had on average one-point higher CSDD score (6.7 (5.3) for participants with dementia, 5.7 (4.7) for participants without dementia), and a higher NPI-total score (15.4 (17.5) for participants with dementia, 9.2 (12.5) for participants without dementia). People with dementia received on average (SD) one less physician-hour per week (3.7 (4.7) hours) compared to residents without dementia (4.7 (4.5) hours).

5.1.2.2 Medication prescriptions

The mean number (SD) of prescribed medication in total ranged between 6.0 (3.2) at baseline and 6.5 (3.1) / 6.5 (3.7) at 6-months follow-up and 36-months follow-up, respectively. The mean number (SD) of psychotropic drugs prescribed in total ranged between 1.2 (1.2) at baseline and 1.5 (1.3) at 6-months follow-up and 18-months follow-up. The prevalence of patients using at least one psychotropic drug was lowest at baseline (62.4%) and highest at 18-months follow-up (73.1%). Among psychotropic drugs, antidepressants had the highest prevalence with a top value at 30-months follow-up and 36-months follow-up (42.2%).

For all the psychotropic drug categories, the highest incidence rates were found between baseline and 6-months follow-up, with the highest values for antidepressants (18.9%), followed by sedatives and hypnotics (17.7%). The highest deprescribing rates were found between baseline and 6-months follow-up, with the highest values for antipsychotics (31.7%) and anxiolytics (31.7%), except for sedatives and hypnotics, with their highest deprescribing rates between 12-months and 18-months follow-up (24.7%).

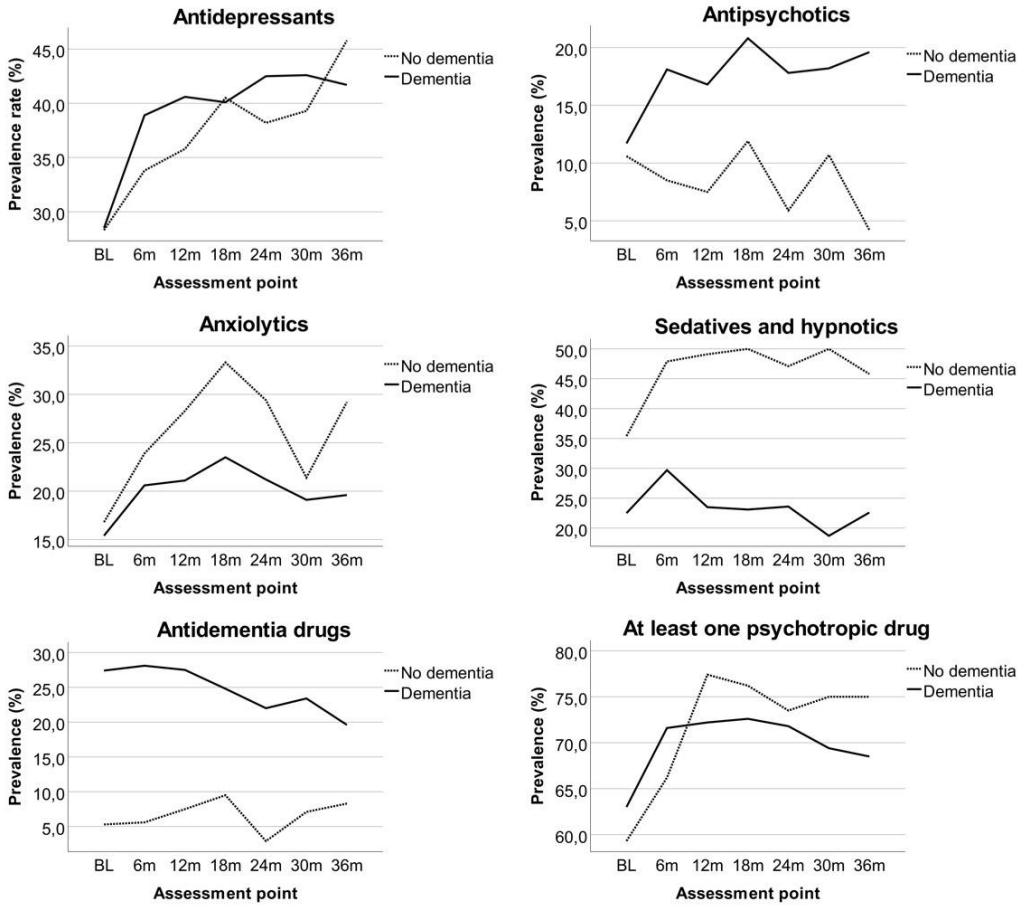
Figures 5.1.2.1 and 5.1.2.2 report a graphical representation of the prevalence-, incidence-, and deprescribing rates for psychotropic drug categories.

5.1.2.3 Results from the regression analyses

The following results focus on the adjusted generalized mixed models. We found no associations between covariates (except for CSDD score) and change in odds over time for the psychotropic drug categories antidepressants, antipsychotics, anxiolytics, sedatives/hypnotics, and antidementia drugs. We found a significant association between CSDD score and change in odds of prescribing sedatives and hypnotics, but only for CSDD scores >8. In this case, the odds of prescribing sedatives and hypnotics increased for higher CSDD scores from baseline to 18-months follow-up, and the odds decreased for higher CSDD scores from 18-months follow-up to 36-months follow-up. We found a significant

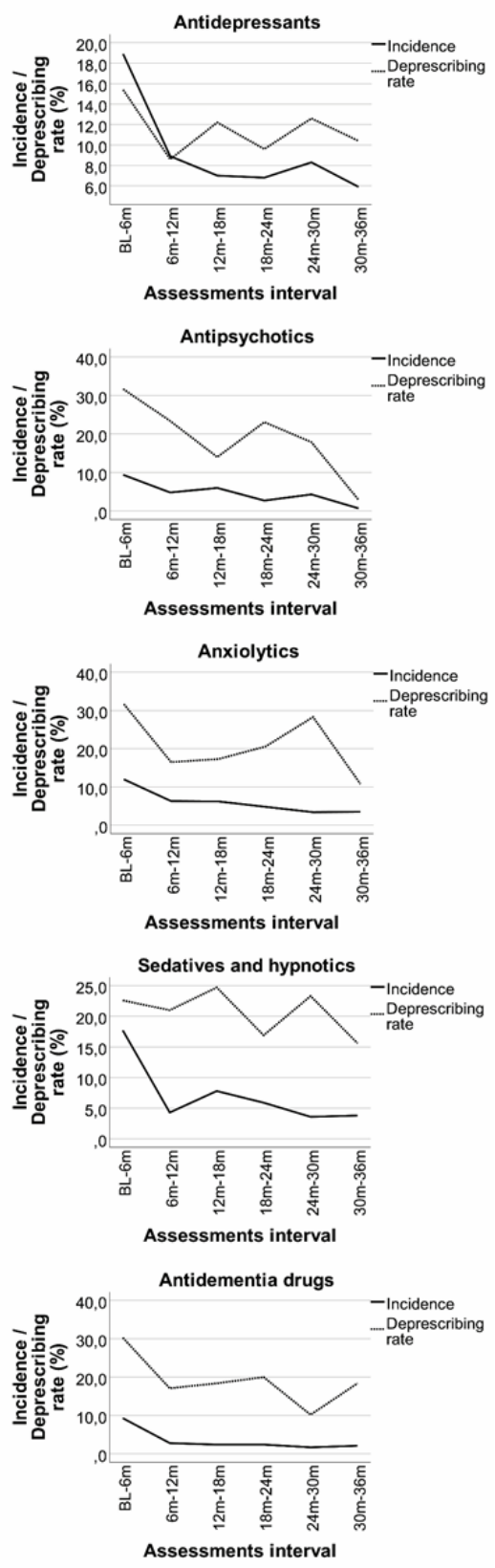
negative association between CDR sum of boxes score and odds of being prescribed sedatives and hypnotics (OR=0.89, 95%CI:0.85-0.94, *p*<0.001). Further, we found a significant association between higher CSDD scores, NPI-affective subsyndrome scores, and being female, with higher odds of being prescribed antidepressants (OR=1.05, 95%CI:1.00-1.10, *p*=0.045; OR=1.09, 95%CI:1.04-1.14, *p*<0.001, and OR=2.09, 95%CI:1,26-3.47, *p*=0.005, respectively). We found a significant association between younger age and odds of being prescribed antidepressants and antipsychotics (OR=0.93, 95%CI:0.90-0.97, p<0.001; and OR=0.96, 95%CI:0.92-0.99, *p*=0.023, respectively). There was a significant positive association between NPI-psychosis subsyndrome scores and odds of being prescribed antipsychotics (OR=1.11, 95%CI:1.05-1.17, *p*<0.001). The odds of being prescribed anxiolytics were significantly higher with increasing NPI-affective subsyndrome scores (OR=1.05, 95%CI:1.01-1.10, *p*=0.026). We found a significant negative association between odds of being prescribed antidementia drug and Charlson comorbidity index scores (OR=0.86, 95%CI:0.75-0.98, *p*=0.023), and between odds of being prescribed antidementia drugs and NPI-apathy subsyndrome scores (OR=0.93, 95%CI:0.86-1.00, *p*=0.039). We found higher odds of being prescribed antidementia drugs in patients living in special care units, compared to patients living in regular or respite and rehabilitation units (OR=1.78, 95%CI:1.09-2.90, *p*=0.021).

Figure 5.1.2.1. Prevalence of psychotropic drug prescriptions from baseline to 36-months follow-up.



Legend: BL Baseline; 6m 6-months follow-up; 12m 12-months follow-up; 18m 18-months follow-up; 24m 24-months follow-up; 30m 30-months follow-up; 36m 36-months follow-up.

Figure 5.1.2.2. Incidence and deprescribing rates of psychotropic drugs, from baseline to 36-months follow-up



Legend: BL Baseline; 6m 6-months follow-up; 12m 12-months follow-up; 18m 18-months follow-up; 24m 24-months follow-up; 30m 30-months follow-up; 36m 36-months follow-up.

5.2 The Effect of the NorGeP–NH on Quality of Life and Drug Prescriptions in Norwegian Nursing Homes: A Randomized Controlled Trial

5.2.1 Main results from paper 3

5.2.1.1 Flow-chart of the trial

Figure 4.2.1 (previous chapter) presents the detailed flow-chart of the study. Nine municipalities in Østfold County agreed to participate in the study, and 603 nursing home residents from 15 nursing homes were assessed for eligibility. Four hundred and thirty-seven residents met inclusion criteria. During eligibility assessment, one nursing home (with 14 residents) withdrew from the study because they lacked local resources to follow up the participants. Further, 161 residents were excluded by drawing lots, 50 residents did not wish to participate, six residents died, one resident moved after inclusion but before baseline assessment, and we excluded two residents due to violation of protocol (the nursing home did not return documentation for the assessments). In total, 217 residents were included and were assessed at baseline. After randomization, 108 residents were allocated in the intervention group (intervention nursing home), while 109 were allocated in the control group (control nursing home). At 12-weeks follow-up, 10 residents in the control nursing homes were lost to follow-up, while 12 residents in the intervention nursing homes were lost to follow up. In the rest of chapter 5.2.1 and 5.2.2, I will use the abbreviations iNHs and cNHs to refer to intervention nursing homes and control nursing homes, respectively.

5.2.1.2 Participants characteristics at baseline

Most participants in both groups were female (71.6% in cNHs, and 56.5% in iNHs), and had comparable age on average (SD) (84.6 (9.4) years old in the cNHs, and 83.3 (8.0) years old in the iNHs). Most participants in the cNHs (56.9%) lived in regular units, while most participants in the iNHs (59.3%) lived in special care units. The participants in cNHs and iNHs lived in units with comparable number of residents, on average (SD) (15.07 (4.41) residents in cNHs, and 13.15 (3.97) residents in iNHs), and with comparable number of staff members per unit on a day shift (4.73 (1.80) staff members in cNHs, and 4.61 (1.79) staff members in iNHs). However, the units in the cNHs where participants lived received on average 0.88 more physician-hours per week compared to the units in the iNHs (on average (SD), 6.43 (1.68) physician-hours per week in the cNHs, and 5.55 (3.52) physician-hours per week in the iNHs). When considering CDR scores, most participants in both groups had dementia (89.3% in the cNHs and 92.3% in iNHs). The two groups had on average (SD) comparable levels of comorbidity measured with Charlson comorbidity index 2.54 (1.96) for cNHs, and 2.57 (1.68) for iNHs), and according to the GMHR, most participants in both groups had a fair general medical health (41.5% in the cNHs and 50.5% in the iNHs). Participants in the cNHs had a slightly lower CSDD score, on average (SD), compared to

iNHs (6.50 (5.84) and 7.46 (5.99), respectively), but comparable GAI score on average (SD) (5.58 (5.70) and 5.0 (5.32) respectively). The average (SD) NPI-total score was higher for participants living in the iNHs (21.92 (21.30)) compared to the cNHs (17.10 (19.10)). Caregivers experienced a higher level of burden measured with NPI-caregiver score in the iNHs (9.48 (10.49)) compared to cNHs (6.92 (8.50)). Both groups had comparable level of functioning measured with PSMS (1.06 (1.31) in the cNHs, and (1.16 (1.29) in the iNHs). Participants in the cNHs had a slightly higher Quality of Life measured with QUALID, on average (SD) compared with participants living in the iNHs (21.31 (6.72) and 23.27 (8.03), respectively). Participants living in cNHs received on average (SD) a lower number of daily medications compared to the iNHs (6.92 (3.49) and 7.55 (3.04), respectively, while both groups had comparable numbers of prescribed pro re nata (PRN) drugs on average (SD) (4.04 (2.74) in the cNHs and 4.72 (2.89) in the iNHs).

5.2.1.3 Primary analyses – change in Quality of Life from baseline to 12-weeks follow-up

For the primary analyses, we estimated a linear mixed model to assess the difference in change in Quality of Life, measured with QUALID. Table 5.2.1.3.1 presents the detailed results of the regression analysis. There was no statistically significant difference between cNHs and iNHs in change in Quality of Life from baseline to 12-week follow-up. We found that the QUALID score remained stable in the iNHs, while QUALID score had a statistically significant increase (which indicated a lower Quality of Life) from baseline to 12-weeks follow-up in the cNHs (p = 0.013).

Table 5.2.1.3.1 Difference in change in Quality of Life, assessed with QUALID, from baseline to 12-weeks follow-up: results from a linear mixed model

	Control NHs	Intervention NHs
Baseline		
n	97	106
Mean (SD)	21.31 (6.72)	23.27 (8.03)
Week 12		
n	84	95
Mean (SD)	22.74 (7.64)	23.11 (8.72)
Mean change (95% CI)	−1.69 (−3.00; −0.38)	−0.18 (−1.43; 1.07)
Mean difference in change (95% CI)	−1.51 (−3.30; 0.28)	
p-value	0.101	

Legends: QUALID, Quality of Life in Late-Stage Dementia; NHs, nursing homes; CI, confidence interval; SD, standard deviation.

5.2.1.4 Secondary analyses – change in other clinical outcomes and prescribed drugs from baseline to 8-weeks and 12-weeks follow-up

We estimated a linear mixed model for continuous variables, and a generalized linear mixed model for categorical variables. Compared to participants in the cNHs, we found a significantly

larger reduction in CSDD score from baseline to 12-weeks follow-up in participants living in the iNHs (mean difference in change (95% CI) −2.59 (−3.95; −1.23), $p < 0.001$). We found a statistically significant reduction in GAI score from baseline to week 8 (−1.69 (−3.37; −0.01), $p = 0.049$) in the iNHs compared to the cNHs. We found that participants in the iNHs had a significantly larger reduction in the odds of having a lower CDR score from baseline to 8-weeks follow-up ($p = 0.007$), but there was no significant difference in the reduction in the same odds from baseline to 12-weeks follow-up.

5.2.2 Additional results from the RCT not included in paper 3

5.2.2.1 Descriptive statistics

Table 5.2.2.1.1 presents the descriptive statistics for psychotropic drug prescriptions during the RCT, for the three assessment points, and dichotomized between "no use" and "use of one or more" specific psychotropic drug category. Antidepressants were the most frequently prescribed psychotropic drug category, with a prescription rate above 30% for all the assessment points in both control and intervention nursing homes.

Table 5.2.2.1.1. Prescription rates of psychotropic drug categories, dichotomized between "no use" and "use of one or more", per allocation group and assessment point

Assessment point		Baseline		8 weeks		12 weeks	
		0, n (%)	1+, n (%)	0, n (%)	1+, n (%)	0, n (%)	1+, n (%)
Antidepressants	**cNHs**	72 (66.1)	37 (33.9)	67 (65.7)	35 (34.3)	64 (64.6)	35 (35.4)
	iNHs	72 (66.7)	36 (33.3)	69 (69.7)	30 (30.3)	67 (69.8)	29 (30.2)
Antipsychotics	**cNHs**	92 (84.4)	17 (15.6)	88 (86.3)	14 (13.7)	86 (86.9)	13 (13.1)
	iNHs	79 (73.1)	29 (26.9)	74 (74.7)	25 (25.3)	71 (74.0)	25 (26.0)
Anxiolytics	**cNHs**	87 (79.8)	22 (20.2)	82 (80.4)	20 (19.6)	80 (80.8)	19 (19.2)
	iNHs	94 (87.0)	14 (13.0)	87 (87.9)	12 (12.1)	85 (88.5)	11 (11.5)
Hypnotics and Sedatives	**cNHs**	79 (72.5)	30 (27.5)	76 (74.5)	26 (25.5)	75 (75.8)	24 (24.2)
	iNHs	86 (79.6)	22 (20.4)	78 (78.8)	21 (21.2)	78 (81.3)	18 (18.8)
Antidementia drugs	**cNHs**	100 (91.7)	9 (8.3)	92 (90.2)	10 (9.8)	88 (88.9)	11 (11.1)
	iNHs	74 (68.5)	34 (31.5)	70 (70.7)	29 (29.3)	67 (69.8)	29 (30.2)

Legend: cNHs Control nursing homes; iNHs Intervention nursing homes.

Notes: for control NHs, N at Baseline/8 weeks/12 weeks was 109, 102, and 99, respectively. For intervention NHs, N at Baseline/8weeks/12 weeks was 108, 99, and 96, respectively.

Table 5.2.2.1.2 presents the prescription rates of a selection of individual psychotropic drugs, divided per allocation group and assessment point. Among antidepressants, escitalopram and mirtazapine were the most frequently prescribed drugs. Haloperidol, risperidone, and quetiapine had comparable rates in the control group throughout the study, while quetiapine had higher prescription rates in the intervention group. Among benzodiazepines and z-

hypnotics, oxazepam and zopiclone had higher prescription rates in the control group throughout the whole study.

Table 5.2.2.1.2. Prescription rates for individual psychotropic drugs, per allocation group and assessment point

	Control nursing homes (N=109/102/99)	Intervention nursing homes (N=108/99/96)
Citalopram		
Baseline, n (%)	4 (3.7)	4 (3.7)
8 weeks, n (%)	4 (3.9)	3 (3.0)
12 weeks, n (%)	5 (5.1)	3 (3.1)
Escitalopram		
Baseline, n (%)	12 (11.0)	19 (17.6)
8 weeks, n (%)	13 (12.7)	13 (13.1)
12 weeks, n (%)	9 (9.1)	11 (11.5)
Mianserin		
Baseline, n (%)	5 (4.6)	4 (3.7)
8 weeks, n (%)	5 (4.9)	3 (3.0)
12 weeks, n (%)	5 (5.1)	2 (2.1)
Mirtazapine		
Baseline, n (%)	18 (16.5)	14 (13.0)
8 weeks, n (%)	15 (14.7)	12 (12.1)
12 weeks, n (%)	15 (15.2)	12 (12.5)
Rivastigmine		
Baseline, n (%)	5 (4.6)	7 (6.5)
8 weeks, n (%)	4 (3.9)	8 (8.1)
12 weeks, n (%)	5 (5.1)	8 (8.3)
Memantine		
Baseline, n (%)	4 (3.7)	25 (23.1)
8 weeks, n (%)	4 (3.9)	21 (21.2)
12 weeks, n (%)	5 (5.1)	21 (21.9)
Oxazepam		
Baseline, n (%)	20 (18.3)	12 (11.1)
8 weeks, n (%)	18 (17.6)	11 (11.1)
12 weeks, n (%)	17 (17.2)	11 (11.5)
Haloperidol		
Baseline, n (%)	5 (4.6)	4 (3.7)
8 weeks, n (%)	5 (4.9)	3 (3.0)
12 weeks, n (%)	4 (4.0)	4 (4.2)
Quetiapine		
Baseline, n (%)	5 (4.6)	15 (13.9)
8 weeks, n (%)	5 (4.9)	12 (12.1)
12 weeks, n (%)	5 (5.1)	13 (13.5)
Risperidone		
Baseline, n (%)	6 (5.5)	6 (5.6)
8 weeks, n (%)	3 (2.9)	6 (6.1)
12 weeks, n (%)	3 (3.0)	5 (5.2)
Zopiclone		
Baseline, n (%)	23 (21.1)	12 (11.1)
8 weeks, n (%)	20 (19.6)	10 (10.1)
12 weeks, n (%)	18 (18.2)	9 (9.4)
Melatonin		
Baseline, n (%)	5 (4.6)	10 (9.3)
8 weeks, n (%)	4 (3.9)	11 (11.1)
12 weeks, n (%)	3 (3.0)	10 (10.4)

Table 5.2.2.1.3 presents the results for the generalized linear mixed model to estimate the odds for change in the use of different psychotropic drug categories. As presented in paper 3, we found no statistically significant difference in the odds for change in psychotropic drugs, between iNHs and cNHs, during the study period.

Further, we estimated a generalized linear mixed model for a selection of specific psychotropic drugs (escitalopram, mirtazapine, memantine, oxazepam, quetiapine, and zopiclone). We found no statistically significant difference in change for the odds of using these specific drugs between iNHs and cNHs during the study period. In a similar way, we estimated linear mixed models for defined daily doses for the same selection of psychotropic drugs. We found no statistically significant difference in change in defined daily doses between iNHs and cNHs from baseline to 12 weeks, except for memantine (mean change (95% CI): 0.23 (0.02; 0.43); p=0.033) (Table 5.2.2.1.4 and Figure 5.2.2.1.1).

Table 5.2.2.1.3. Results from the generalized linear mixed model for psychotropic drug categories, dichotomized.

	Antidepressants		Antipsychotics		Anxiolytics		Hypnotics and Sedatives		Antidementia drugs	
Parameter	Regr. coeff. (SE)	p-value	Regr. coeff. (SE)	p-value	Regr. coeff. (SE)	p-value	Regr. coeff. (SE)	p-value	Regr. coeff. (SE)	p-value
Intercept	-0.99 (0.37)	0.007	-2.24 (0.42)	<0.001	-1.96 (0.41)	<0.001	-1.35 (0.36)	<0.001	-3.33 (0.55)	<0.001
Baseline – ref.										
Week 8	0.004 (0.43)	0.993	-0.36 (0.53)	0.501	-0.06 (0.50)	0.905	-0.21 (0.43)	0.633	0.27 (0.66)	0.687
Week 12	0.04 (0.43)	0.935	-0.40 (0.54)	0.456	-0.17 (0.51)	0.740	-0.23 (0.44)	0.608	0.49 (0.65)	0.449
Intervention NHs										
(Control – ref.)	0.04 (0.51)	0.934	0.86 (0.55)	0.120	-0.59 (0.61)	0.331	-0.55 (0.54)	0.304	2.23 (0.66)	0.001
Week 8 x iNHs	-0.29 (0.59)	0.626	0.20 (0.68)	0.765	-0.12 (0.76)	0.874	0.29 (0.64)	0.652	-0.48 (0.79)	0.541
Week 12 x iNHs	-0.30 (0.60)	0.623	0.31 (0.69)	0.654	-0.17 (0.78)	0.822	0.05 (0.66)	0.942	-0.68 (0.79)	0.385
	cNHs	**iNHs**	**cNHs**	**iNHs**	**cNHs**	**iNHs**	**cNHs**	**iNHs**	**cNHs**	**iNHs**
Odds for change (95% CI)										
Baseline to week 8	1.00 (0.43; 2.33)	0.75 (0.34; 1.68)	0.70 (0.25; 1.98)	0.86 (0.37; 1.98)	0.94 (0.35; 2.51)	0.83 (0.27; 2.57)	0.81 (0.35; 1.90)	1.09 (0.43; 2.73)	1.30 (0.36; 4.74)	0.80 (0.34; 1.89)
Baseline to week 12	1.04 (0.44; 2.42)	0.77 (0.34; 1.74)	0.67 (0.23; 1.93)	0.91 (0.39; 2.10)	0.85 (0.31; 2.28)	0.71 (0.22; 2.25)	0.80 (0.34; 1.89)	0.84 (0.32; 2.17)	1.64 (0.46; 5.86)	0.83 (0.35; 1.95)
Odds for difference in change	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Baseline to week 8	0.75 (0.23; 2.40)	0.626	1.23 (0.32; 4.65)	0.765	0.89 (0.20; 3.93)	0.874	1.33 (0.38; 4.67)	0.652	0.62 (0.13; 2.90)	0.541
Baseline to week 12	0.74 (0.23; 2.41)	0.623	1.36 (0.35; 5.27)	0.654	0.84 (0.18; 3.84)	0.822	1.05 (0.29; 3.81)	0.942	0.51 (0.11; 2.35)	0.385

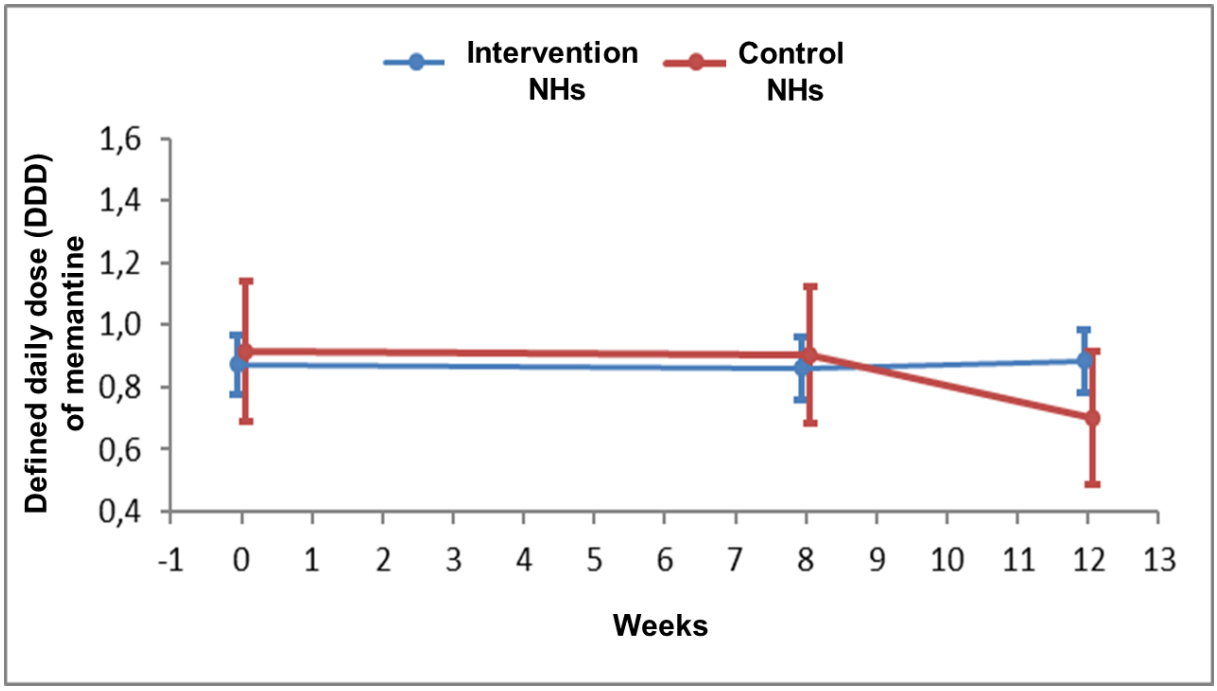
Legend: CI Confidence interval; cNHs Control nursing homes; iNHs Intervention nursing homes; OR Odds ratio; Regr. coeff. Regression coefficient; SE Standard error

Table 5.2.2.1.4. Results from the linear mixed model for defined daily doses (DDDs) of memantine.

Parameter	Regression coefficient (SE)	p-value
Intercept	0.92 (0.12)	<0.001
Baseline – ref.		
Week 8	-0.01 (0.07)	0.868
Week 12 12	-0.22 (0.09)	0.026
Intervention nursing homes (Control – ref.)	-0.04 (0.13)	0.741
Week 8 x Intervention nursing homes	-0.002 (0.08)	0.984
Week 12 x Intervention nursing homes	0.23 (0.10)	**0.033**
	cNHs	**iNHs**
Mean change (95% CI)		
Baseline to week 8	0.01 (-0.13; 0.15)	0.01 (-0.05; 0.08)
Baseline to week 12	0.22 (0.03; 0.40)	-0.01 (-0.09; 0.07)
Difference in change	Mean (95% CI)	p-value
Baseline to week 8	-0.002 (-0.16; 0.15)	0.984
Baseline to week 12	0.23 (0.02; 0.43)	**0.033**

Legend: cNHs Control nursing homes; iNHs Intervention nursing homes; SE Standard error

Figure 5.2.2.1.1. Graphical representation of the results in Table 5.2.2.1.4.



Legend: NH Nursing home.

6.0 Discussion of the main findings

The overall objectives of this thesis are:

1) to present the course of psychotropic drug prescriptions in Norwegian nursing homes from admission and over a three-year period;

2) to examine which clinical and environmental factors may explain changes in prescription rates over time in nursing home residents;

3) to test the effectiveness of NorGeP-NH, in a real-world situation, on Quality of Life, other clinical outcomes, and prescriptions in nursing home residents.

Paper 1 and 2 are related to objectives 1) and 2), while paper 3 is related to objective 3). Subchapter 6.1 to 6.3 report the discussion of the main findings for the three papers.

6.1 The course of psychotropic drug prescriptions from nursing home admission over time

Both paper 1 and paper 2 used data from the REDIC-NH project (Roen et al., 2017). Thus, the results are estimated from the same cohort, but differ slightly due to the different number of included participants in the analyses. In paper 1, we focused on the prescription rates of psychotropic drugs in residents with dementia at admission, and how prescriptions changed during the first six-months of their stay. In paper 2, we examined prescription rates in all nursing home residents, differentiating prescription rates for residents with and without dementia, in a longer time frame, from admission and during the following three years of the residents' stay. In this paper, we focused on both prescription- and deprescribing rates. I will first discuss the results from the descriptive statistics, pointing out similarities and differences with other studies. I will then discuss which clinical and environmental factors we have found to be correlated to particular psychotropic drug prescriptions, and which possible clinical implications these results may have.

6.1.1 Overall prescription of psychotropic drugs

Our studies found that the prescription of psychotropic drugs in newly admitted nursing home residents was frequent. In paper 1, we found that 67.5 % of the residents with dementia received at least one psychotropic drug at nursing home admission. The prevalence significantly increased to 74% six months later (p = 0.008). In paper 2, we also found a high prevalence rate for psychotropic drugs in all nursing home residents, which never dropped below 62.4% during the whole follow-up period. Interestingly, the lowest rate was measured at baseline. These results are in line with data found in a Swiss study, where 70.8% of newly

admitted residents with dementia received at least one psychotropic drug (Lustenberger et al., 2011). Differently, a Norwegian study published in 2001, found a considerably lower prevalence for any psychotropic drug at nursing home admission (24%) (Nygaard, 2001). I do not have a clear explanation for this discrepancy between the results in Nygaard's study and ours, but our higher psychotropic drug prescription rates are in line with other Norwegian cross-sectional studies (Gulla et al., 2016; Ruths et al., 2013; Selbaek et al., 2017) and one longitudinal study (Helvik et al., 2017). However, a recent meta-analysis pointed out that there is a high variability in the results across different studies describing prescription patterns, also partially due to the different definitions of what a psychotropic drug is (Jester et al., 2021). For example, most of the referred Norwegian studies in this chapter defined psychotropic drugs as all drugs in the ATC classification system under the N05 and N06 groups, while Lustenberger's study did not include antidementia drugs in the analyses. These differences might not be clinically important, as most of the studies describing prescription patterns report a high prescription rate of psychotropic drugs across countries. I will now focus on the different psychotropic drug categories.

6.1.2 Antidepressants

In both paper 1 and paper 2, we found that antidepressants were the most frequently prescribed psychotropic drug at admission. In paper 1, we found that 31.0% of residents with dementia received antidepressants at admission, and the rate significantly increased to 40.1% six months later. In paper 2, we found that the prevalence rate remained high and above 40% in residents with dementia from 12-months follow-up until 36-months follow-up. In line with the results of paper 1, paper 2 described the highest incidence rate for antidepressants in people with dementia (19.1 % in paper 1, and 19.2 % in paper 2) between admission and 6-months follow-up. Deprescribing rates in residents with dementia were at their highest between baseline and 6-months follow-up (14.6%). In paper 2, we found that prescriptions rates for antidepressants for residents with and without dementia were comparable during the follow-up period.

Comparable prevalence rates can be found in other Norwegian studies. Iden and colleagues, for example, found that after admission to a nursing home, about 44% of residents received antidepressants, where 33% of these residents had an antidepressants-therapy initiated before admission (Iden et al., 2014). Similarly, international studies presented a generally high prescription rate for antidepressants at nursing home admission. In Australia and in Belgium, 29.5% and 35.8% of newly admitted nursing home residents received antidepressants, respectively (Ivanova et al., 2018; O'Connor et al., 2010). In France, 44.5% of people with dementia received antidepressants at nursing home admission (Rolland et al., 2012). Also in Switzerland, it was common for people with and without dementia to receive

antidepressants at nursing home admission (29.6% and 26.7%, respectively) (Lustenberger et al., 2011).

The frequent prescription of antidepressants at nursing home admission may on one hand reflect the continuation of an antidepressant therapy initiated before nursing home admission (Iden et al., 2014), and on the other hand, it might be explained by the need of antidepressants upon nursing home admission, prescribed right after an initial evaluation of the nursing home physician. Depression, with or without anxiety, is common in older adults newly admitted to a long-term care facility (Ulbricht et al., 2019).

Following the dramatic increase in the prescription rates of antidepressants during the first six months, we found that the prevalence curve became less steep, also reflected in a higher incidence rate between admission and 6-months follow-up, compared to the other assessment intervals. Ivanova and colleagues, in contrast, found that the prescription rates of antidepressants remained stable in Belgian nursing homes from admission and during a two-year follow-up (Ivanova et al., 2018). Our results may be explained by a prompt pharmacological intervention to treat depression right after admission. A recent cross-sectional large population study conducted in the US, showed in fact that up to 35.3 – 48.5% of residents with depression and/or anxiety did not receive psychiatric treatment upon NH admission (Ulbricht et al., 2019). Nursing home physicians might then initiate a therapy with antidepressants right after admission, to treat or mitigate depressive symptoms that have become evident. This is a good clinical practice, considering that detecting and consequently treating depression, might decrease mortality in nursing home residents (Damian et al., 2017). However, it is still concerning that from one-year follow-up and further on, the prevalence rates for antidepressants remained at high levels. This might partially be explained by either the fact that residents are in continuous need of antidepressants, or by the fact that there is a lack of continuous effect evaluation for these medications prescribed for depressive symptoms. If antidepressants were prescribed mainly to treat depression, it would still be difficult to justify high prescription rates over time, since antidepressant do not have high efficacy in treating depression in dementia, and dementia is common in nursing home residents (Dudas et al., 2018; Helvik et al., 2015). However, antidepressants may be used off-label to treat insomnia or agitation in people with dementia. To support this explanation, a Norwegian study examining neuropsychiatric symptoms in the same cohort we cited in paper 1 and 2, showed that depression, agitation, and night-time behaviour, among other neuropsychiatric symptoms, were common and persistent from admission and during a 30-months follow-up (Helvik et al., 2018). The results from Helvik's study were in line with results from another study conducted in the Netherlands (van den Brink et al., 2020). The presence of night-time behaviour or agitation might then contribute to the

widespread prescription of antidepressants over time. Despite the lack of studies examining the off-label use of antidepressants in older adults, a recent German study showed that the off-label prescription of antidepressants in older adults is fairly common (Schäfer et al., 2021). Antidepressants may then be widely prescribed for other purposes than depression, such as in the treatment of agitation in dementia (Porsteinsson et al., 2014).

6.1.3 Antipsychotics

Compared to antidepressants, antipsychotics were less frequently prescribed in people with dementia at nursing home admission (13.5% in paper 1, 11.7% in paper 2). The prescription rates, however, increased significantly in people with dementia six months after admission, reaching a level of 19.0% (paper 1) and 18.1 % (paper 2). In line with the results for antidepressants, antipsychotics were most frequently initiated or discontinued between admission and 6-months follow-up. In paper 2, we found that the prevalence rates for antipsychotics were higher in residents with dementia compared to residents without dementia, throughout the study period. Comparing our results with international studies, antipsychotics were less frequently prescribed at nursing home admission than in Australia (27.1%) (O'Connor et al., 2010), Canada (28.3% in women and 33.8% in men) (Maclagan et al., 2020), Switzerland (28.4%) (Lustenberger et al., 2011), or Belgium 28.5% (for the comparative group, 25.7%) (Ivanova et al., 2018). Our prevalence results were also lower compared to results in another Norwegian longitudinal nursing home study (Helvik et al., 2017), yet comparable with a Norwegian cross-sectional study (Gulla et al., 2016), and with data from the US (The U.S. Centers for Medicare & Medicaid Services, 2022). Another Norwegian cross-sectional study analysed changes in antipsychotic prescriptions in nursing home residents between 2004 and 2011 (Selbaek et al., 2017). In the mentioned study, the prevalence rate found in 2004/2005 was higher than the values we found in our study, while the rate found in 2010/2011 was comparable with our results (Selbaek et al., 2017).

The high variability between different studies might simply reflect different cultural aspects regarding prescriptions of antipsychotics in nursing home residents. Antipsychotics may indeed be used to control acute and severe neuropsychiatric symptoms, such as agitation, aggression, or delusion, but this still raises concerns regarding their safety when prescribed in older adults with dementia, due to the increased risk of adverse effects (Tampi et al., 2016). National authorities have warned physicians and healthcare personnel to show precaution in using antipsychotics in older patients with dementia (Norwegian Directorate of Health, 2017). However, antipsychotics are still the intervention involved in the larger number of studies concerning the treatment of neuropsychiatric symptoms, despite their moderate efficacy and severe side-effects (Bessey & Walaszek, 2019). A commonly cited

recommendation is to treat patients with antipsychotics for the shortest possible time (Bessey & Walaszek, 2019; Tampi et al., 2020).

After an initial increase in the prescription of antipsychotics from nursing home admission to six months, the prevalence remained stable during the three-year follow-up. This is also reflected by the highest incidence between admission and 6-months follow-up (10.5% in people with dementia, paper 2). When examining the incidence curve visually, there seems to be a decreasing trend for both incidence and deprescribing rates over time. The incidence rates found in our studies, are slightly higher than the results from a Canadian study, where the incidence rate for antipsychotics during the first six months after nursing home admission was 7% (Foebel et al., 2015). The authors, however, excluded patients with psychiatric disorders, schizophrenia, Tourette's syndrome, Huntington's disease, and hallucinations, and patients with depression who needed antipsychotics as augmenting therapy (Foebel et al., 2015). Our incidence rates were also higher compared to an Australian study (5.4% between admission and six months) (O'Connor et al., 2010), yet comparable to the results from a Swiss study where the incidence rate of antipsychotics prescription was 10.7% during the first six months after nursing home admission, with decreasing incidence rates during a 18-month follow-up period (Lustenberger et al., 2011).

The results we found in our studies might reflect several aspects of the treatment of neuropsychiatric symptoms over time. One could think that the antipsychotic treatment is effective to minimize severe neuropsychiatric symptoms. However, neuropsychiatric symptoms such as delusions, hallucinations, and agitation, seem to be persistent over time (Helvik et al., 2018), and become more severe the longer the resident stays in the nursing home (Helvik et al., 2016). This might partially justify the continuous prescription of antipsychotics over time, but it still stands in contrast to national and international guidelines. Another explanation for the significant increase in prescription rates for antipsychotics during the first six months, and a flattening prevalence curve over time, might also be explained by a more prompt pharmacological evaluation right after admission, and a lack of frequent reviews over time. Finally, one should not underestimate other factors that might contribute in the change (or lack of change) in antipsychotics prescriptions over time, such as how well nursing home healthcare personnel is trained, the degree of belief healthcare personnel and residents' next of kin have in the effect of antipsychotics, the fear of symptom worsening and decreased Quality of Life after antipsychotics discontinuation (Azermai et al., 2014; Thompson Coon et al., 2014).

6.1.4 Anxiolytics, sedatives, and hypnotics

In our studies, we found that the prescription of anxiolytics, and in particular of sedatives and hypnotics, were frequent. For both categories, people without dementia had higher prevalence rates compared to people with dementia during the whole follow-up period. For anxiolytics, the prevalence rates ranged between 15.7% at baseline, and 24.6% at 18-months follow-up (values for the whole nursing home population). These results were higher compared to prevalence rates found in an Australian study, where daytime anxiolytics were prescribed in 6% of residents at admission (O'Connor et al., 2010). In our study, we found that for sedatives and hypnotics, up to 50% of residents without dementia, and up to 29.7% of residents with dementia received these drugs. In relation to time, there was no significant change in prescription rates for sedatives and hypnotics, which is also reflected visually in Figure 5.1.2.1. A positive result was that besides a higher incidence rate for sedatives and hypnotics during the first six months of the stay, under 10% of residents were newly prescribed sedatives and hypnotics during the rest of the follow-up intervals. Another positive result was that deprescribing rates ranged between 15.6% and 24.7% during the three-year follow-up, which might reflect a constant attention towards tapering and deprescribing these drugs..

Similar high prevalence rates were found in a Belgian study, where 43.3% (comparative group prevalence 43.0%) of newly admitted residents received benzodiazepines, with a slight, but not significant, decrease two years later (41.5%) (Ivanova et al., 2018). In addition, the same authors described signs of deprescribing for antipsychotics and benzodiazepines in people who developed dementia, or had dementia from admission, compared to people without dementia (Ivanova et al., 2018). It is difficult to properly compare these results with our papers, but I have made some considerations. People with dementia received anxiolytics, sedatives, and hypnotics less frequently during the whole study period, compared to people with dementia. As discussed in paper 2, differences between studies reporting the use of sedatives might be explained by several factors: the individuality of each resident, the environmental culture of the ward where a resident lives, or in other prescription cultures, such as the use of other forms of sedative medications rather than benzodiazepines / benzodiazepine-like drugs (i.e. sedating antipsychotics). This last factor may be supported by a Danish registered-based study, where the authors found that the prescription of sedating medication, in particular benzodiazepines and z-hypnotics, increased dramatically six months prior to nursing home admission, decreased after admission, but were compensated by an increase in the prescription of other sedating psychotropic drugs (Pottegård et al., 2021). However, compared to Pottergård and colleagues, our studies showed lower prescription rates for sedatives, hypnotics, and antipsychotics in people with dementia, which would not

explain a mutual effect-compensation. I would also point out that the higher prescription rates in people without dementia derived from relatively low numbers, as residents without dementia were in fact a minority (N=24/192 at 36-months follow-up).

6.1.5 Antidementia drugs

Antidementia drugs are prescribed to people with a dementia disorder (such as Alzheimer's disease or Lewy body dementia) that can respond to the treatment with either cholinesterase inhibitors, or memantine. Considering that most residents participating in the REDIC-NH study had dementia, it is not surprising that this group had the highest prevalence of prescriptions of antidementia drugs. The prevalence of antidementia drugs prescription in people with dementia was at its highest at six months after admission (28.1%), and it decreased slightly during the follow-up period. The slight decrease may be explained by the fact that physicians and nursing home staff considered the benefit of these drugs no longer to be present, leading to tapering and deprescribing, according to national guidelines (Norwegian Directorate of Health, 2017). A minority of residents that were evaluated by researchers not to have dementia, were still prescribed antidementia drugs (below 10% during the whole follow-up period). One possible explanation is that there is a discrepancy between the research dementia diagnosis set by the authors, and the clinical evaluation of nursing home physicians. Another explanation might be that a small number of residents who did not meet the criteria for dementia, still had some signs of cognitive decline, leading physicians to prescribe antidementia drugs in hope of giving their patients some symptom reduction. In the total nursing home population, the prevalence of antidementia drugs was never above 25.1% during the whole follow-up period, reflecting that these drugs might still not be appropriate for most people whose dementia has become so severe that they need to live in a nursing home.

6.2 Clinical and environmental factors associated with psychotropic drugs prescriptions

In the analyses of paper 1 and 2, we explored which clinical and/or environmental factors could be associated with higher or lower prescription rates of psychotropic drugs over time. This is important to identify groups of residents or group of symptoms that might need monitoring over time, or to identify if particular environmental factors, such as the size of a nursing home unit, or the availability of nursing home physicians, may explain changes in prescription rates.

Residents with more severe affective symptoms at admission had higher odds of being prescribed antidepressants, which is not surprising, as antidepressants are commonly

prescribed to treat depression. Residents with more severe affective symptoms had also higher odds of receiving anxiolytics throughout the study period. Anxiety is a common symptom in depression, and anxiolytics may be prescribed to mitigate depression characterized by predominant anxiety symptoms. Benzodiazepines are the most common types of anxiolytics prescribed in nursing homes, with oxazepam being the most frequently used (Gulla et al., 2016). People with depression receiving benzodiazepines might need monitoring, both right after being prescribed anxiolytics and over time. There is no strong evidence that the long-term use of benzodiazepines in older adults is effective to treat anxiety (Markota et al., 2016). Since benzodiazepines are associated with a higher risk of dependence, falls, fractures, cognitive decline, and mortality in older adults, it might be wise to have a plan for prompt tapering and discontinuation as soon as they are not considered necessary anymore (Markota et al., 2016). Nursing home residents with more severe affective symptoms at nursing home admission also had higher odds of receiving sedatives and hypnotics both at admission and six months later. Among sedatives, zopiclone is the most common prescribed drugs in nursing homes (Gulla et al., 2016). This is a drug prescribed to treat insomnia, and it may be prescribed in nursing home residents with depression who suffer of sleeping problems. However, zopiclone and other similar drugs (often referred as z-hypnotics) are not recommended in older adults as they do not seem to improve sleep latency and duration (American Geriatrics Society, 2019). Residents with depression and sleeping problems should then be carefully assessed in order to avoid prolonged sedatives prescription, and as soon as they are prescribed z-hypnotics, there should be a plan for evaluating the effect and discontinuing the medication. An interesting result discussed in detail in paper 2, was how the odds of being prescribed sedatives increased for more severe depressive symptoms the first 18 months after nursing home admission, but the same odds decreased for more severe depressive symptoms from 18 months and after. This might be a sign that physicians are more prone to prescribe sedatives during the first period after a nursing home admission, in those residents with more severe depression, but tend not to prescribe sedatives in residents with depression who have been living for a longer period in the nursing home, due to the lack of effect or risk of side effects.

Residents with dementia had higher odds of receiving antidepressants with increasing severity of the psychotic symptoms. One possible explanation is that psychotic symptoms may be concomitant with depression, which is treated with antidepressants rather than antipsychotics. Another explanation might be that antidepressants are used to control behaviour, such as agitation, caused by psychosis (Kongpakwattana et al., 2018; Porsteinsson et al., 2014).

During the whole study period we also found that with increased dementia severity, residents had lower odds of being prescribed sedatives and hypnotics. This is a positive result as people with mild cognitive impairment and dementia are at high risk of developing complications caused by sedatives-hypnotics (Schroeck et al., 2016). Thus, our results might reflect a more cautious prescribing of sedatives in people with severe cognitive impairment.

It is common for nursing home residents to be multimorbid (Reilev et al., 2019). In paper 1 we found that people admitted with a higher level of comorbidity were at lower risk of receiving antidepressants both at admission and six months later. This might be explained by the fact that physicians are cautious in prescribing drugs with possible severe side effects to persons with multiple diseases. However, patients with multimorbidity at admission should be carefully evaluated for depression, as depression is highly frequent in persons with multimorbidity (Stordal et al., 2003). Detecting depression in nursing home residents might be crucial to improve the prognosis. Resident whose depression is not identified and treated seem to have a higher mortality risk compared with residents without depression, or with residents whose depression is diagnosed and properly managed (Damian et al., 2017). Additionally, in paper 2 we found that residents with higher comorbidity had lower odds of being prescribed antidementia drugs. This result might be explained by the fact that nursing home residents with high comorbidity are considered to have a lower prognosis and shorter life expectancy, where consequently, antidementia drugs may have lower efficacy. A Swedish registry-based cross-sectional study showed for example that among people with Alzheimer's disease, younger persons receiving a lower number of medication (as a proxy for lower co-morbidity) were more likely to receive antidementia drugs (Fereshtehnejad et al., 2014), supporting this hypothesis. However, other studies have shown that antidementia drugs may have a positive effect on mortality and life expectancy (Wu et al., 2015; Xu et al., 2021).

In paper 2, we found that residents with a more severe level of apathy had lower odds of receiving antidementia drugs. Apathy is a common neuropsychiatric symptom in people with dementia, and it is defined in neurocognitive disorders as the presence of diminished initiative, interest, and emotional expression and responsiveness (Miller et al., 2021). This syndrome may not be as distressing in a nursing home environment as other neuropsychiatric symptoms, such as agitation or aggression, and physicians might not be compelled to prescribe medications to treat this neuropsychiatric symptoms. However, a recently published review presenting different pharmacological approaches to treat apathy in dementia, mentioned that cholinesterase inhibitors may improve apathy, and propose cholinesterase inhibitors as a possible first medication choice, after trying to manage apathy with non-pharmacological interventions (Azhar et al., 2022).

In paper 1, we found no nursing home characteristics associated with the prescriptions of psychotropic drugs. In paper 2, we found that residents living in special care units had a positive association with prescriptions of antidementia drugs. This association may be expected, considered that special care units are offered to residents with a more severe degree of dementia and higher need of continuous care, where antidementia drugs may be used to mitigate dementia symptoms. The other nursing home characteristics included in the analyses (unit size, number of staff members per unit working dayshift, number of hours a physician was available per unit during a week (for paper 2)) had no significant associations with psychotropic drug prescriptions. Previous studies exploring possible associations between nursing home characteristics and psychotropic drug prescriptions have shown differing results. In the Netherlands, the number of staff per patient was inversely related to antidepressants prescriptions, while hypnotics were positively associated with number of patients per living room (Zuidema et al., 2011). In Croatia, residents living in bigger nursing homes had a higher risk of receiving antipsychotics, while residents under the care of a physician with more working experience had lower risk to receive antipsychotics and anxiolytics (Petek Šter & Cedilnik Gorup, 2011). A large cross sectional study examined data of over 5000 nursing home residents in Germany and Austria, and found no statistical significant associations between prescription of psychotropic drugs and nursing home characteristics, such as number of bed per nursing home, number of residents under the care of one physician or proportion of trained nurses (Richter et al., 2012). In France, nursing home residents living in facilities with a larger number of physicians (>30/100 beds) had a greater risk of receiving antipsychotics inappropriately, where appropriateness was defined by a specific algorithm developed for the study (Laffon de Mazières et al., 2015). The methodology and examined nursing home characteristics vary among the mentioned studies. The comparison across the studies may be difficult. However, the overall impression is that there is no strong evidence of a recurrent nursing home characteristic that may explain higher or lower risk of psychotropic drug prescriptions.

6.3 The influence of NorGeP-NH on Quality of Life, other clinical factors, and prescription rates

6.3.1 The choice of Quality of Life as primary outcome

Quality of Life in people with dementia has been given particular attention in the past few years. Quality of Life embraces broad aspects of a person's life and may give an idea of a person's self-perceived disease burden, or how a person responds to a particular type of care. Quality of Life is indeed subjective, and an individual's perception of their physical and

psychological health, social interactions, environment and economic factors, beliefs, and level of independence (WHO Centre for Health Development, 2004). The World Health Organization underlines that as a person gets older, Quality of Life is determined by the person's ability to access needed resources, as well as maintaining autonomy and independence (WHO Centre for Health Development, 2004). Physical and psychological health are two defined factors included in the definition of Quality of Life, but is there a direct correlation between the Quality of Life and the level of disease? One would think that a larger disease burden and a more severe disability automatically leads to lower Quality of Life. This, however, is not necessarily true. Quality of Life has in fact been studied within the "disability paradox" concept, that is, the discrepancy between the level of disability in one person and the Quality of Life a person perceives (Albrecht & Devlieger, 1999). There are persons with more severe disability and a higher perceived Quality of Life, and vice versa, persons with lower level of disease burden and lower Quality of Life. It seems that the perceived Quality of Life is more connected to how a person can establish a balance between body, mind, spirit, and environment, despite their disability (Albrecht & Devlieger, 1999). This is probably easier to examine in people with the capacity to express their thoughts and feelings, and more difficult in people with cognitive impairment. However, focusing on Quality of Life in people with lower cognitive functioning is still important in order to optimize treatment and care. A recent systematic review of 56 different studies has summarized factors correlated with Quality of Life in older adults with dementia. Among many other factors, polypharmacy and psychotropic polypharmacy was found to reduce the Quality of Life in older people with dementia, which may be explained by the direct effect of medication on a person's Quality of Life or the effect of multiple diseases on Quality of Life, where polypharmacy may be a proxy for comorbidity (Jing et al., 2016). Quality of Life in nursing home residents with dementia has previously been found to be associated to neuropsychiatric symptoms, particularly agitation and depression, cognitive decline, and psychotropic drug use (Wetzels et al., 2010). Thus, we thought that Quality of Life would be an important and relevant outcome to examine, in relation to the performed intervention described in paper 3.

6.3.2 The choice of NorGeP-NH as intervention tool

The intervention performed and described in paper 3, was aimed primarily at nursing home physicians and their knowledge about psychotropic drug management in older nursing home residents. As presented in chapter 2.5, there is a high variability in studies reporting the effect of interventions to reduce psychotropic polypharmacy, and not all interventions may be beneficial. NorGeP-NH was developed specifically for nursing home residents, but as presented in chapter 2.4, it has never been tested in a real-world situation to evaluate the

effect of this explicit PIM list on resident's clinical outcomes. However, NorGeP-NH is suggested as a tool to perform a medication review by Norwegian authorities (Norwegian Directorate of Health, 2012). NorGeP-NH has been proven effective to discover PIM in nursing home residents (Halvorsen et al., 2019), but less effective to detect preventable severe adverse drug events compared to the explicit list STOPP (Wang-Hansen et al., 2019). However, its potential does not necessarily translate into clear effectiveness in a clinical setting, which is why we decided to test this in a randomized controlled trial.

6.3.2 The effect of a medication review performed with NorGeP-NH on nursing home residents' Quality of Life

The intervention described in paper 3 and reported in chapter 4.2.4, was aimed at nursing home physicians in the intervention group. Physicians learned about pharmacology and psychopharmacology in older adults, and how to perform a medication review using NorGeP-NH. Further, nursing home physicians performed a medication review by using what they learned in the lecture, and the structure / guidelines of NorGeP-NH. Three months after the intervention, we did not find a significant difference in Quality of Life between residents living in the intervention nursing homes and the control nursing homes. Our results are in line with the results presented in another Norwegian RCT conducted in nursing homes (COSMOS) (Husebo et al., 2015). In COSMOS, medication reviews were part of a complex intervention. The authors found no significant changes in the Quality of Life in the intervention group four months after the intervention was carried out (Husebo et al., 2015). Similarly to our results, a Cochrane review found that it is not certain that medication reviews improve Quality of Life. However, the quality of evidence for this result was low, and supported by few studies (Alldred et al., 2016).

Our results lead to a series of considerations. To begin with, the lack of significant change in Quality of Life between the two groups may be explained by the fact that the study itself had a short duration. Possible effects on Quality of Life due to medication changes performed after a medication review may need time to manifest, and it may not be visible at 12-weeks follow-up. Some drugs, for example the benzodiazepine diazepam or the SSRI fluoxetine and paroxetine, have a long half-life, and side effects may be present during a tapering process and even after a total drug discontinuation.

Another possible explanation is that a medication review alone does not affect Quality of Life, simply because Quality of Life embraces a larger number of factors, which are not necessarily connected to the amount or type of medication a person receives. Thus, a medication review may have a positive effect on Quality of Life when implemented with other interventions that meet different needs in a nursing home resident. This is in line with the

discussed “disability paradox” in chapter 6.3.1 (Albrecht & Devlieger, 1999). The COSMOS project, for example, showed that a multi-component intervention (including medication review) did in fact positively affect Quality of Life in nursing home residents, but only several months after the intervention ended (Husebø et al., 2019).

A final possible factor that may explain our results, is that the intervention itself had no effect on Quality of Life at all. However, we did find some interesting results within the two different groups. In the intervention group, Quality of Life remained stable, while in the control group, Quality of Life worsened significantly during the follow-up period. One may speculate that without applying NorGeP-NH, residents in the intervention group would have shown the same worsening in Quality of Life that we found in the control group. In the intervention group, most of the residents lived in special care units. These units are often dedicated to residents with larger disease burden and more severe dementia. In this population one would expect a rapid decline in functioning, a more rapid symptom worsening over time, and indirectly a worsening in Quality of Life. The stable Quality of Life we found in the intervention group, may demonstrate a possible effect of NorGep-NH in maintaining Quality of Life stable. However, one should not forget that Quality of Life was measured with QUALID, which is a proxy-based assessment tool, and therefore reflects the caregivers’ individual evaluation, and not the participants’ own perception of Quality of Life. The lack of blinding of the intervention may have affected the evaluation of the caregivers that performed the assessments. This aspect is further discussed in chapter 7.0. It is also important to mention that most of the residents in the intervention nursing homes lived in special care units. These units may have person-centred psychosocial activities optimized for residents with severe disease, which may itself slow down a more rapid worsening in Quality of Life. However, a 10-month follow-up study conducted in Norwegian nursing homes did not show a significant difference in Quality of Life (measured with QUALID, among other assessment tools) between residents living in regular units compared to residents living in special care units over time (Mjørud et al., 2014).

6.3.3 The effect of a medication review performed with NorGeP-NH on nursing home residents’ other clinical outcomes

Other clinical outcomes used in the study are presented in chapter 4.2.5. We found few, yet still important, significant changes during follow-up, between the intervention nursing homes and the control nursing homes.

First, we found that residents in the intervention nursing homes, compared to the control nursing homes, showed an improvement in depression scores from baseline to 12-weeks follow-up. This might be explained by the fact that a medication review leads to an

optimization in a resident's pharmacotherapy, possibly reducing drugs that cause side-effects, discomfort, and consequently more severe depressive symptoms. As presented in chapter 5.2.2, we found no significant changes in prescription of antidepressants during the follow-up period. However, we did not analyse in detail the prescription of somatic drugs that may have depressive symptoms as adverse effect. In paper 3, we discussed the potential of several drug categories to give depression as an adverse outcome. Antihypertensives, proton pump inhibitors, and analgesics are among the most common drug categories that may lead to depressive symptoms as a potential adverse effect (Qato et al., 2018). Further, depression seems more likely to be present in people using three or more drugs that have depression reported as a potential adverse effect (Qato et al., 2018). It might be that NorGeP-NH decreased the amount of prescribed somatic drugs with depression as a potential side effect, even though we did not analyse this aspect in detail. It might also be that residents whose medication was changed after the medication review had a hope for change, influencing depressive symptoms in a positive way. For the same reason, healthcare personnel assessing the level of depression in the intervention nursing homes may have been affected by the knowledge of medication changes carried out after a medication review, leading to a more positive change in depression scores. This is also further discussed in chapter 7.0.

Second, residents in the intervention nursing homes, compared to the control nursing homes, showed a temporary increase in the CDR scores and a temporary reduction in anxiety symptoms measured with GAI. The temporary increase in CDR scores, which corresponds with a more severe dementia, may simply be an arbitrary result, without any significant clinical explanation. However, most residents in the intervention nursing homes lived in special care units, which offer care to people with severe dementia symptoms, and with a poor prognosis. The temporary increase in CDR scores may then reflect the physiological course of dementia. The temporary reduction in anxiety may be explained by the fact that people received attention during the assessments, and they knew their medication may be changed or reviewed for the better, leading to some symptom relief.

6.3.3 The effect of a medication review performed with NorGeP-NH on nursing home residents' medications

The effect of NorGep-NH on the total medication prescription in the residents living in the intervention nursing homes was only temporary, as we found a significant decrease from at 8-weeks follow-up, but not at 12-weeks follow-up. This result might have different explanations.

Some drugs may have been temporarily discontinued and then reintroduced because the residents' symptoms worsened. This is not an uncommon practice, and symptom worsening in residents with multimorbidity and polypharmacy may happen after drug discontinuation. Another explanation is that NorGeP-NH may have contributed to optimize a resident's pharmacotherapy, but without being translated into a reduction of the total amount of drugs prescribed. Appropriateness is not a synonym of the number of drugs a person receives, and polypharmacy may indeed be appropriate, as presented in the introduction section (chapter 2.4.1) (World Health Organization, 2019). Increasing appropriateness, for example, may also mean that some omitted, but necessary drugs, are introduced. However, there is a clear consensus that polypharmacy in older adults is associated with a wide series of adverse effects that require monitoring (Pazan & Wehling, 2021). NorGeP-NH may optimize a patient's medication, yet not shown by the number of medications a resident receives. Medication reviews may positively influence drug appropriateness (Beuscart et al., 2017) However, the total number of drugs a resident uses, may alone not be a sufficient indicator of drug appripriateness. NorGeP-NH can discover potentially inappropriate medication that may cause severe adverse drug events (Wang-Hansen et al., 2019), but could be used in combination with other implicit tools, such as MAI (Hanlon et al., 1992), to measure the real clinical appropriateness of pharmacotherapy in a nursing home resident. However, a recent Cochrane review presented that medication review tools seem not to have a clear effect on drug prescriptions in older adults (Rankin et al., 2018). This is also in line with recently published results from a RCT, where a multi-profession medication review conducted in care homes, increased the appropriateness of medication in people aged 65 or older, but failed to show any significant improvement in clinical outcomes (Desborough et al., 2020).

NorGeP-NH did not influence the prescription of psychotropic drugs. These results are in line with studies presented in chapter 2.5. There is a high variability in the methods used to reduce psychotropic drug prescription in older adults. Medication reviews that focus specifically on psychotropic drugs may reduce the amount of psychotropic drug prescriptions in older adults. However, even such reductions do not seem to have significant clinical impacts (Sheehan et al., 2018). NorGeP-NH contains guidelines concerning prescriptions of certain psychotropic drug categories, and physicians in the intervention group attended a lecture on psychopharmacology in older adults. However, it might still be challenging for nursing home physicians to carry out tapering and discontinuation of psychotropic drugs fearing that symptom may worsen. Further, any intervention aimed to modify pharmacotherapy may encounter several barriers, such as how well personnel is trained, or simply the willingness of personnel, physicians, or the patient, to carry out a medication change at all (Rankin et al., 2018). Additionally, a single intervention may not be enough to

modify prescription practice in nursing homes. A previous literature review and meta-analysis showed that medication reviews and educational interventions were effective to reduce prescription of hypnotics, but had no effect on antipsychotics prescriptions (Nishtala et al., 2008). However, the authors found that the effectiveness was greater in those interventions with several educational sessions compared to interventions with a single session (Nishtala et al., 2008). Conducting a medication review right after nursing home admission, particularly with the cooperation between physician, pharmacists, and legal representatives, might be more effective (Blenke et al., 2018). The same study found that an early medication review right after admission had a high implementation rate three months after the intervention, when 84.8% of the medication changes implemented after the review were still effective at 90-day follow-up (Blenke et al., 2018).

NorGeP-NH did not affect the daily dosage of psychotropic drugs, except for memantine. Most psychotropic drugs were in fact continued without significant changes. Memantine dosages were significantly lower in control nursing homes after 12 weeks, compared to intervention nursing homes. One would imagine that NorGeP-NH could reduce the prescriptions of antidementia drugs in the intervention nursing homes residents. Cholinesterase inhibitors are mentioned in NorGeP-NH as medication to be considered for tapering and discontinuation (criterion 30). Memantine is not specifically mentioned in NorGep-NH, but it may still be considered a medication with preventive effect (criterion 34). This criterion suggests that all medication with preventive effect should be considered for tapering and discontinuation (Nyborg et al., 2015). However, the daily dosage of memantine significantly decreased after 12 weeks only in the control group. A possible explanation can be found by examining differences in the two groups at baseline. At baseline, more people in the control nursing homes had mild dementia compared to in the intervention nursing homes, and less people had moderate and severe dementia compared to the intervention nursing homes. Memantine is prescribed to people with moderate to severe dementia. Thus, residents in the intervention nursing homes might have been in more need of memantine, because of their dementia diagnosis and severity, compared to residents living in control nursing homes. Even though significant, the reduction in the Defined Daily Dose Memantine in control nursing homes from baseline to 12 weeks was of 22%, which corresponds to 4.4 mg, and might not be clinical important.

7.0 Methodological considerations

In this chapter I will discuss both the strengths and the limitations concerning the three papers in the thesis. Some topics are connected to a specific paper, while other topics regard methodological issues encountered in all the three studies. I will therefore present these issues in the following subchapters.

7.1 The longitudinal aspects of paper 1 and paper 2

Paper 1 and 2 present results from a longitudinal cohort study conducted in Norwegian nursing homes. As far as we know, REDIC-NH was the first study conducted in Norway including nursing home residents from admission, following them up with frequent assessments every six months, and over a long period (Roen et al., 2017). The frequent assessments, including the registration of prescribed medication, are a strength of the study. Frequent assessments give a better insight in how prescribing practices change over time in the same population, in relation to clinical characteristics. Longer assessment intervals may decrease the ability to uncover important information about clinical and prescription changes. The longitudinal design also gives the possibility to understand which clinical characteristics at previous assessment points may influence further prescriptions practices. This is important for all nursing home residents, and particularly for groups of residents with higher odds of being prescribed medications that need close and frequent monitoring. However, the longitudinal design comes with several limitations.

To begin with, a longitudinal study in an already frail and multimorbid population, is expected to have participants dropping out. A previous study using the same data from the REDIC-NH study, estimated that in Norwegian nursing homes, about 25% of the residents died during the first year after admission (Sandvik et al., 2016). In paper 2, we lost 422 out of 504 residents over a period of three years because of death, which gave a natural loss of data during follow-up. A high attrition rate may raise concerns about attrition bias (Nunan et al., 2018). We did partially address this issue in paper 1, by analysing differences between residents lost to follow-up after the baseline assessment, and residents who remained in the study. Residents who were lost to follow-up had poorer physical health, higher comorbidity, higher CSDD scores, and lower Quality of Life. Some of these factors may be associated with residents being in a terminal phase of their disease, approaching death. In paper 2, we did not analyse possible significant differences between residents who remained in the study and those who dropped out. We argued therefore that there might be associations that were lost in our estimations.

Further, missing data has been an issue that we addressed in both paper 1 and paper 2. In both papers, missing was managed by imputation, and we could include more residents in the analysis. In paper 2, we argued that by using a generalized linear mixed model, we reduced possible bias caused by missing data, to some extent.

A third issue we encountered was related to the variable “dementia status at baseline”. A research dementia diagnosis was given by two researchers that analysed all the data available at baseline. However, cognitive impairment is usually progressive, and more residents during the follow-up may have fulfilled dementia criteria compared to what baseline data indicated. We did not evaluate this in detail for each assessment point. However, we did use CDR as a proxy score to evaluate if cognitive impairment was present, and in which severity, and included this variable in the regression analyses for paper 2.

Further, because of the low number of residents included in the last follow-up assessments, the calculated prescribing rates for the last assessment points in paper 2 were based on very few residents. In paper 1, the chosen outcome variable was *change in prescription rates* for psychotropic drugs from baseline to six months. However, such type of variable was more difficult to handle when rates were based on very small numbers during the last follow-ups for paper 2. Therefore, in paper 2, we decided to use *change in odds for prescribing* a psychotropic drug category as outcome variable, and we estimated associations with covariates during the whole follow-up period.

Finally, even though not directly related to the longitudinal design of paper 1 and 2, another issue addressed was whether the distribution of residents among the included nursing homes may have had significant differences, and whether these possible differences may have influenced the results. However, in the regression analyses we included the size and type of nursing home unit to find possible association with these characteristics and changes in psychotropic drug prescriptions. In the estimated results, no nursing home characteristics included in the analyses were associated with psychotropic drug prescriptions, except for special care units, which were significantly associated with prescriptions of antidementia drugs (paper 2).

7.2 The choice of inclusion and exclusion criteria for paper 1 and paper 2

Paper 1 and paper 2 differed slightly regarding exclusion criteria. In paper 1, we focused on changes in prescriptions during the first six months from nursing home admission, and particularly for people with dementia. We also analysed differences between people who had a dementia research diagnosis compared to those who were evaluated not to have

dementia. Because of this, we found that it was appropriate to exclude seven residents from the analyses who did not have data on dementia diagnosis. The probable reason for these missing data was that the researchers who gave a dementia diagnosis to the participants of the REDIC-NH study (Roen et al., 2017), could not assess a resident's cognitive state with the available information in the collected data. In paper 2, we had a broader focus on psychotropic drug prescriptions in nursing home residents, during a longer period. Dementia status at baseline was still a variable that we considered for analyses, but it was not the main focus of the paper. However, we did a new investigation in the original paper data set, and we were able to fill in dementia status for those residents who did not have any data available during the analyses conducted for paper 1. For paper 1, this is a clear limitation, even though only seven residents were excluded because of this issue. However, we improved the quality of the data for paper 2 to include as many residents as possible in the analyses. Similarly, in paper 1 we excluded from analyses all those residents who did not have prescribed medication registered at baseline. This a limitation of the REDIC-NH study, because it was not possible to know whether the lack of registered prescribed medication was due to poor data collection, or in the best case scenario, the fact that a resident was not prescribed any medication. In paper 2, we did not exclude these patients from the analyses, and assumed instead that the lack of registered medication meant that the patient did not use medication at all. In this case we decided to accept a certain level of uncertainty, without excluding possible residents who actually were not prescribed medications.

7.3 The choice of assessment tools and assessments performed by nursing home staff

Assessing nursing home residents may be challenging, particularly when residents have a severe cognitive impairment. Collecting information about residents' mental health may be particularly difficult when the residents have a reduced capacity of self-introspection, or a reduced capacity to verbalize how they feel. This is one of the main reasons why many assessment tools used for both the first two papers, and for paper 3, were proxy-based. The choice of using proxy-based assessment tools has both strength and limitations. The tools used are validated and used in Norway and internationally, both in research and in clinical practice. They are based on structured items to be assessed, and they are meant to be performed by healthcare personnel. Healthcare personnel are required to have a theoretical knowledge about what they must assess, and an individual knowledge of the resident to be assessed. Some of the assessment tools require a long observation time. As an example, the Clinical Dementia Rating scale (CDR) (Morris, 1993), requires that the healthcare personnel have observed the residents for the four weeks prior to the assessment. It is

therefore both necessary, and unavoidable, to involve nursing home staff in the mentioned assessments. This leads to a higher number of assessors and a possible higher variability in the obtained calculated scores. The alternative would be using fewer external assessors, but this would be both demanding and unpractical. In both studies (REDIC-NH for paper 1 and 2, and the RCT for paper 3), we tried to minimize the variability among assessors by giving selected healthcare personnel standardized training. This gave a common theoretical background for the different assessment tools, for the clinical aspects which the assessors were supposed to observe, and practical skills in order to perform the assessments. However, the assessors may still have been biased while performing the assessments. This is particularly important to take into consideration for paper 3. The lack of blinding after the intervention started, may have led the healthcare personnel to over- or underestimate clinical aspects connected to the knowledge of a possible medication change after a medication review. For example, the knowledge that some medications were tapered or discontinued after performing NorGeP-NH, may have led the assessor to be particularly attentive to the consequences of the tapering or discontinuation. Despite this risk of bias, we still believe that the use of proxy-based tools performed by nursing home staff who know the residents well, was a better choice than using external assessors. External assessors may too have under- or overestimated certain clinical aspects, which require a deep knowledge of a resident's clinical picture, and its complex nuances.

Despite most of nursing home residents have a certain degree of cognitive impairment, in the RCT study reported in paper 3, we decided to use some assessment tools that required cooperation of the resident. For example, to assess depression, we decided to use both the proxy-based Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), and the patient-based Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979). Unfortunately, this led to several missing data points, as MADRS was probably difficult to perform in persons with a reduced capacity to understand the questions, and to give reliable answers. This led to a low response rate, where only 78/109 (71.6%) of the residents living in control nursing homes, and 45/108 (41.7%) of the residents in the intervention nursing homes could respond to MADRS at baseline. During the follow-up assessments, the response rates were even lower. This is an important limitation concerning the use of resident–based assessment tools in participants with cognitive impairment, which needs to be taken into consideration when interpreting the results. Using a combination of proxy-based and resident-based tools to assess one clinical aspect may minimize possible skewed results, but it is an important aspect to consider when designing assessment methods in a vulnerable population. The more assessment performed, the

higher the burden this may cause in a resident who must respond to more questions or perform more tasks.

Finally, I would comment on the use of resident-based tools to assess a resident's cognitive impairment. For the REDIC-NH study, which paper 1 and 2 are derived from, the Mini-Mental State Examination (MMSE) was used (Folstein et al., 1975). MMSE has received critiques about its lower ability to detect mild cognitive impairment (Nasreddine et al., 2005; Wind et al., 1997). Therefore, during the designing stage of the RCT, which paper 3 derived from, the authors and the research group decided to use a different tool, the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). This decision was also supported by a Cochrane review, pointing out the limitations of MMSE in recognising small cognitive changes in people with mild cognitive impairment (Arevalo-Rodriguez et al., 2015). However, similarly to the limitations discussed for other patient-based assessments earlier in this chapter, MoCA requires cooperation of the resident, which was not possible to achieve for all the participants. In fact, only 79/108 (73.1%) and 73/109 (67.0%) of the residents in the control nursing homes and intervention nursing homes respectively, were able to perform MoCA at baseline. Thus, the results estimated from this assessment, should be interpreted cautiously.

7.3.1 QUALID versus other assessment tools to examine Quality of Life, and issues related to the use of QUALID score as a primary outcome

As discussed in chapter 6.3.1, Quality of Life embraces several aspects of a person's physical, mental, and spiritual life that is particularly challenging to assess in people with a lower capacity to express their thoughts and feelings due to dementia. Thus, it was important to find an assessment tool that could, to some extent, help clinicians and nursing home staff assess residents with cognitive impairment in the most reliable way as possible. During the design stage of the RCT, we related to a recently published study which concluded that the Norwegian version of the Quality of Life in Late-Stage Dementia (QUALID) was reliable and valid (Roen et al., 2015). QUALID is a proxy-based tool that embraces different observation items, such as how a person's mood appears, the expressions of comfort or discomfort in different situations, and how a person appears in basic life situations (Weiner et al., 2000). This is indeed limitative, and dependent on the items / aspects that require observation and the interpretation of these, which do not embrace all the aspect of a person's Quality of Life. This limitation is probably present for other assessment tools approaching Quality of Life. A recent systematic review, for example, presented QUALID as one of five assessment tools used in literature to describe / report Quality of Life in people with dementia (Burks et al., 2021). Similarly to QUALID, the Alzheimer Disease-Related Quality of Life (ADRQL) (Rabins et al., 1999), and QUALIDEM (Ettema et al., 2007), are also proxy-based assessment tools

performed by healthcare professionals. On the other hand, the Quality of Life in Alzheimer Disease (QUAL-AD) and DEMQOL are assessment tools based both on proxy observations and self-report (Ettema et al., 2007; Logsdon et al., 2002). Burks et al. presented QUALID as a tool suitable for institutionalized people, which is in line with our choice. However, the mentioned review points out several limitations related to the solely use of a proxy-based tool to assess Quality of Life. For example, challenging behaviour (the authors use depression and irritability as an example) may be estimated to play a larger role in reducing Quality of Life when evaluated only by proxy, compared to what self-reported scores may show (Burks et al., 2021). Additionally, it seems that proxy-based tools do not consider pain and comorbidity as influential for Quality of Life, compared to what self-reporting tools may show (Burks et al., 2021). Finally, studies comparing proxy-based and self-reported tools, show that proxy-based tools consistently report a lower Quality of Life, compared to what a person with dementia may perceive (Burks et al., 2021). For future research, it might be wise to use both self-reported and proxy-based tools to assess broader factors related to a person's Quality of Life.

When choosing QUALID as a primary outcome, we also encountered some challenges for the power calculation of the RCT. At the time of the design stage of this RCT, we were not aware of any conducted study using QUALID as a primary outcome, where specific changes in QUALID scores were used in the power calculation. We found one previously published Norwegian study protocol, where QUALID was chosen as a primary outcome; however, for the power calculations, the authors used NPI-NH instead of QUALID (Husebo et al., 2015). In the power calculation of our RCT, we defined a change in QUALID score of 33% as clinically important. We argued that this defined change was necessary to make sure that changes derived from our intervention were clinically important. However, and for future research, I would argue that a 33% change in QUALID score is highly optimistic in a nursing home population with a high level of morbidity, and would reconsider the definition of what a clinical important change in QUALID score may be, even if this may cause a higher needed number of included participants in a RCT.

Finally, I would comment on the choice of QUALID score as a primary outcome assessed 12 weeks after baseline. The time frame of our RCT may be argued being too short. Medication changes carried out after a medication review may require time to show their effect on clinical outcomes and Quality of Life in nursing home residents. For example, a previously mentioned Norwegian study showed that a multi-intervention in nursing home residents had a positive effect on Quality of Life only several months after the intervention was performed (Husebø et al., 2019). However, nursing home residents are multimorbid, and several clinical events and pharmacological changes may happen during a short period, independently of a

performed medication review. Therefore, we decided that the duration of our RCT was appropriate to avoid many confounding factors influencing Quality of Life of the participants.

7.4 Registering medication prescriptions and related issues

For paper 1 and 2, we used data deriving from the REDIC-NH study (Roen et al., 2017). Data about prescribed medication was collected, but it had several limitations. To begin with, only data about daily prescribed medication was registered with its ACT-code. Data concerning *pro re nata* drugs was not collected. Information about pro re nata drugs is challenging to manage. A long list of prescribed pro re nata drugs reflects only the potential of prescribing those medications, and not the actual administering. Further, the registration methods of what is actually administered also vary from unit to unit, making a structured data collection difficult to achieve. However, pro re nata drugs are an important aspect of pharmacotherapy in institutionalized residents. Some pro re nata drugs may actually be administered regularly. Even if this aspect is difficult to detect, for the RCT we decided to collect data about the number of pro re nata drugs a resident was prescribed. Even with a high uncertainty on the actual drug administration, the total number of pro re nata drugs may still give some information about the potential total medication burden a resident is exposed to.

In the REDIC-NH study, the assessors were asked to register both the regular medication a resident received, together with the daily dosages. Unfortunately, the quality of the data registered about the dosages was poor, and we decided to discard that aspect from the analyses. However, daily dosages are very important from a clinical perspective. This is why in the RCT, we focused on collecting precise data on daily dosages for every medication registered, and we analysed in detail changes in the defined daily doses. Medication reviews do not only require evaluation of whether or not a resident needs a medication, but also if the daily dosage is adequate in relation to its effect and adverse effects. For example, a person receiving 10 mg escitalopram, may have a clear effect on depression, but also show serotonergic adverse effects. A medication review may in this case lead to a reduction in the daily dosage to reduce adverse effects. Collecting data on dosages and focusing on related changes, and not only if a medication is discontinued or not, is clinically relevant.

7.5 The choice of RCT, real-world situation, efficacy, and effectiveness of an intervention

When designing a method to test our intervention, we chose an RCT as it is a gold standard design. RCTs are highly controlled designs which test the efficacy of an intervention, but it may not necessarily give an answer to the intervention's effectiveness. The efficacy of an intervention can be defined as how well an intervention performs in a controlled experiment such as an RCT, while effectiveness may be defined as how well this intervention performs in a real-world situation (Nordon et al., 2016). Authors have been conceptualizing the term "efficacy-effectiveness gap" to underline the differences between a controlled experiment conducted in a "sterile" environment, and a real-world environment, influenced by factors that are often difficult to control, yet have a strong impact in how well an intervention performs. This conceptualization is not meant to discard RCTs as valid designs, but to best design RCTs by acknowledging and considering important factors that may influence the efficacy-effectiveness gap (Nordon et al., 2016; Thompson, 2021). I will use here Nordon and colleagues' conceptualization and paradigms to explain the challenges encountered in developing and performing our RCT in nursing homes.

To begin with, the choice of a cluster-RCT was made to avoid contamination bias. It would have been difficult to perform an intervention addressed to nursing home physicians, if the whole nursing home was not treated as a cluster. This raised some issues during the development of the study, and the recruitment of nursing homes and physicians willing to participate. There is in fact a high variability in how municipalities and nursing homes are organized. Some municipalities have a rotation system where different physicians work in different nursing homes. Other municipalities have nursing home physicians working part-time in the nursing homes, and the rest as a general practitioner / family doctor. Some nursing homes had their own physician working in defined units, but physicians participated at clinical meetings with other nursing home physicians. The risk of contamination here may be high. We tried to minimize contamination by making sure that physicians in one cluster did not interact with physicians in another cluster. It was particularly important to define a cluster based on how / where physicians worked. As an example, one municipality had an intra-municipality collaboration / rotation system for the nursing home physicians, so all the nursing homes in that municipality were treated as one cluster.

The behaviour of physicians, and healthcare personnel, is discussed as one important paradigm that unavoidably influences the outcome of an intervention (Nordon et al., 2016). A physician's knowledge, belief, scepticism, level of training, may all influence how well an intervention performs in a real-world situation. Our intervention tried to give physicians a common level of training to minimize gaps on the level of knowledge about pharmacology

and psychopharmacology. However, we decided to let physicians, with the collaboration of nursing home staff, make the final decisions about medication prescriptions after a review. In this way, the study reflected more the practice that is usual in a daily care-setting. For the same reason, a resident's adherence to a therapy (or therapy change) may strongly influence the outcome of an intervention. We decided to let possible medication changes be implemented after a review solely by the decision of a physician and after a discussion of therapy with their patients. Finally, under the behaviour-paradigm, the differences in resources in a care-setting (in our case nursing homes), may be highly important. For example, a medication change may have led to negative clinical changes, but higher resources in a nursing home unit could compensate and mask negative effects of the intervention.

A second paradigm highlighted by Nordon and colleagues, is the design and/or method used to assess the efficacy of an intervention (Nordon et al., 2016). In this case, the authors mention blinding and placebo/active comparator as factors. In our case, blinding was not possible during the whole study period. We kept the knowledge of allocation blinded at the beginning of the study to make sure baseline assessments were not influenced by the knowledge of being in the intervention or control group. However, once the intervention started, it would have been impossible to conceal this from the assessors. The very knowledge of having performed / not performed a medication change may influence what a healthcare personnel would observe clinically, and as a consequence of that influence the results of clinical assessments. For example, a healthcare professional fearing that a resident's depression may worsen, knowing that antidepressants were tapered and discontinued, may have led to an increased focus in depression symptoms, and consequently possible higher depression scores during the follow-up period. Possible positive clinical changes of our intervention may then have been masked by a negative impact of healthcare personnel observation / fear. This is indeed hypothetical, but still an important aspect to consider when assessing less "tangible" symptoms and signs related to mental health, yet highly connected to the real-world practice when the observed symptoms and signs are unavoidably influenced by the individual healthcare professional's perception.

Further, it has been argued that RCTs have limited generalizability, since RCTs do not include real-world populations, do not reflect clinical routines or use outcomes that are nor clinically relevant (Nordon et al., 2016). We did consider these aspects when designing our RCT. First, we decided to include the general nursing home population, reducing the exclusion criteria to a minimum. Participants were excluded mainly when the inclusion and performance of evaluations would be considered highly unethical. Thus, we decided not to include participants who were suffering of severe physical and / or mental diseases, where

assessments and possible medication changes would have caused severe distress. Otherwise, potential participants would be considered for inclusion. Second, besides giving NH staff and physicians lectures, we let physicians and staff decide how to perform NorGeP-NH, using their own internal routine / practice, and without interfering. This was important to keep the local clinical routines as similar as possible to the usual nursing home practice. Third, we decided to use Quality of Life as a primary outcome, and focus on other clinical outcomes that are highly relevant for clinical practice.

Finally, the third paradigm described by Nordon and colleagues, refers to the increased variability and interactions in a real-life population and its direct influence on the effect of an intervention (Nordon et al., 2016). Specifically, this is not much different from the other aspects discussed until now, but it underlines the importance of anticipating factors that are unavoidable when testing the effect of an intervention in a study population. These factors may be genetics, physiology, morbidity, nutrition, physical health, environmental factors, and behavioural factors (such as off-label prescriptions, beliefs of effect /non-effect, adherence to a therapy, etc.). Removing some of these factors from the design of a RCT may modify its results, which would not be easy to apply to a real-world situation (Nordon et al., 2016). This is why we used the term “real-world” clinical setting in previous discussions, to underline that our RCT tried to test the effect of a medication review by including, as much as possible, a common nursing home population, without interfering more than necessary with how the intervention and the assessments were conducted, reflecting the normal clinical daily routine in a nursing home practice.

8.0 Conclusions and possible implications

This thesis presents a comprehensive description of how psychotropic drugs are prescribed in nursing home residents from admission and during a longer period. Already at admission, over 60% of residents received at least one psychotropic drug. The psychotropic drugs categories most frequently prescribed were antidepressants, sedatives, and hypnotics. During the first six months stay, we observed a dramatic increase in the prescriptions of most psychotropic drugs categories. From six months and during a 3-year follow-up, over 70% of residents with- and without dementia received at least one psychotropic drug. Throughout the whole study period, antidepressants were the most frequently prescribed psychotropic drugs in residents with dementia. Sedatives and hypnotics were prescribed in up to 50% of residents without dementia between six months and three years from nursing home admission.

Further, we have explored which clinical and environmental factors could explain psychotropic drug prescriptions in nursing home residents. Particularly for residents with more severe affective symptoms, we found that they had a higher risk of receiving antidepressants, anxiolytics, and sedatives / hypnotics. However, other clinical factors seemed to be associated with lower odds of receiving psychotropic drugs. For example, people with more severe dementia received fewer sedatives and hypnotics, antidepressants were less frequently prescribed in people with higher comorbidity, and antidementia drugs were less prescribed in people with a higher level of apathy. We found only one environmental factor associated with the prescription of antidementia drugs, which was people living in special care units. The comparison with national and international studies highlights the high variability in prescription practices of psychotropic drugs in nursing home residents. We argued that medication appropriateness should be frequently evaluated to optimize psychotropic drug prescriptions.

Finally, we tested the effectiveness of a structured medication assessment tool developed in Norway. The effect of this assessment tool has never been tested before in a clinical setting. We performed a cluster-randomized controlled study to assess whether NorGep-NH performed by nursing home physicians was able to improve the residents' Quality of Life, and psychological and physical health, and possibly reduce the amount of prescribed psychotropic drugs. Our study showed a limited effect of NorGep-NH in a real-world situation, both on the residents' Quality of Life, mental health, physical health and medication prescriptions. Therefore, we concluded that this structured medication assessment tools may be used as an aid, but it may not be replaced by an individual interdisciplinary clinical evaluation of a nursing home resident.

This thesis shows that nursing home residents are highly exposed to psychotropic drugs. Considering that most nursing home residents have dementia, and psychotropic drugs may have a limited effect to treat neuropsychiatric symptoms, psychotropic drugs require a careful and frequent evaluation in the nursing home population, to avoid unnecessary prescribing over time. Many structured medication assessment tools, included NorGep-NH, show a limited effect on the prescription of psychotropic drugs. There may be the need to develop more specific tools to be used in nursing homes to evaluate the necessity and/or appropriateness of psychotropic drugs.

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Original Study

Does Psychotropic Drug Prescription Change in Nursing Home Patients the First 6 Months After Admission?

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A B S T R A C T

Objectives: To explore the course of psychotropic drug (PTD) prescription from admission (BL) to 6-month follow-up (6m) in Norwegian nursing homes (NHs). To examine how clinical variables, such as neuropsychiatric symptoms (NPS), cognition, physical health, and NH characteristics at BL are associated with prescription rates at 6 months.
Design: An observational longitudinal cohort study (data from the Resource Use and Disease Course in Dementia—Nursing Home study) designed to examine the course of dementia, psychiatric and somatic diseases, and drug prescriptions in NH patients during the first 6 months after admission.
Setting and Participants: We included 696 patients at admission to 47 representative Norwegian NHs.
Methods: Demographic and clinical characteristics at BL and 6m are presented. Dementia severity was assessed by the Clinical Dementia Rating scale and the Functional Assessment Staging of Alzheimer's Disease scale. Final diagnosis was made by 2 of the authors (G.S. and S.B.) according to ICD-10 criteria. Prevalence, incidence, and persistence rates of PTD prescriptions for people with dementia are presented. Generalized mixed models were used to identify possible predictors for the course of PTD prescription from BL to 6m.
Results: Prescription rates of antidepressants, antipsychotics, anxiolytics, sedatives, and hypnotics increased in people with dementia from BL (67.5% received at least 1 PTD) to 6m (74.0% received at least 1 PTD). Younger age and higher Neuropsychiatric Inventory—affective subsyndrome score at BL were associated with higher odds of antidepressant prescription, whereas patients with higher comorbidity at BL had lower odds of receiving antidepressants, both at BL and 6m. Higher Neuropsychiatric Inventory-affective subsyndrome scores at BL were associated with higher odds of sedative and hypnotic prescription at both assessment points.
Conclusions and implications: PTD prescription rates increase from BL to 6m. Medication appropriateness should be frequently evaluated after admission to optimize PTD prescriptions.

Cognitive impairment, dementia, and functional decline are risk factors for admission to a nursing home (NH).[1,2] People with dementia represent 84% of the NH population admitted for long-term care in Norway.[3] Neuropsychiatric symptoms (NPS), such as depression, anxiety, and delusions, are common in NH residents with dementia,[4,5] and are often treated with psychotropic drugs (PTDs) over time.[6] Antidepressants are still widely used to treat depression in Alzheimer's disease, but few studies are available to make

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conclusions about their effectiveness.[7] Antipsychotics are also commonly prescribed, despite their low efficacy and a variety of adverse outcomes.[8]

Antipsychotics, benzodiazepines, and anticholinergic medications can be potentially inappropriate for older people,[9] meaning that these medications might have an unfavorable balance between benefits and harms.[10] It is alarming that in Norway, almost half of the patients living in NHs receive potentially inappropriate medication,[11] and among them PTDs are widely prescribed.[6]

Even if several studies have described the high prevalence of PTD prescription in NHs,[12–16] few studies have extensively explored the longitudinal aspect of PTD prescription from admission and during the first months stay.[17,18] Furthermore, differences in the methodological approach and choice of study population make it challenging to compare results from different studies. This longitudinal aspect is particularly important to understand which clinical and environmental factors might be associated with PTD prescription over time, to identify possible risk groups at admission, and to promptly target specific pharmacologic or nonpharmacologic interventions.

The aim of this article was to present the PTD prescription rates in older individuals with dementia at admission to Norwegian NHs and 6 months after admission. We examine whether NPS, cognition, and psychological symptoms at admission were associated with prescription rates at 6 months' follow-up (6m), and we describe the differences in prescription rates between people with and without dementia.

Methods

Data were collected through the Resource Use and Disease Course in Dementia—Nursing Home (REDIC-NH), a longitudinal cohort study designed to examine the course of dementia and other psychiatric and somatic diseases in NH patients from admission until death.[19]

Participants

We included 696 patients at admission to 47 representative Norwegian NHs. Inclusion criteria were as follows: (1) 65 years or older; (2) younger than 65 years could participate if established dementia; (3) expected stay at the NH > 4 weeks; and (4) life expectancy >6 weeks.

REDIC-NH Data Collection and Selection

Baseline (BL) data were collected between March 2012 and November 2014, within a month of admission to the NH. Follow-up data were collected every 6 months.

Figure 1 shows the flow chart. We excluded all patients with no medication registered at BL (n = 18) or at 6m (n = 8) because we could not differentiate participants who were not prescribed medication from those with missing data on this variable. Seven patients had no data regarding dementia diagnosis and were excluded. Of the

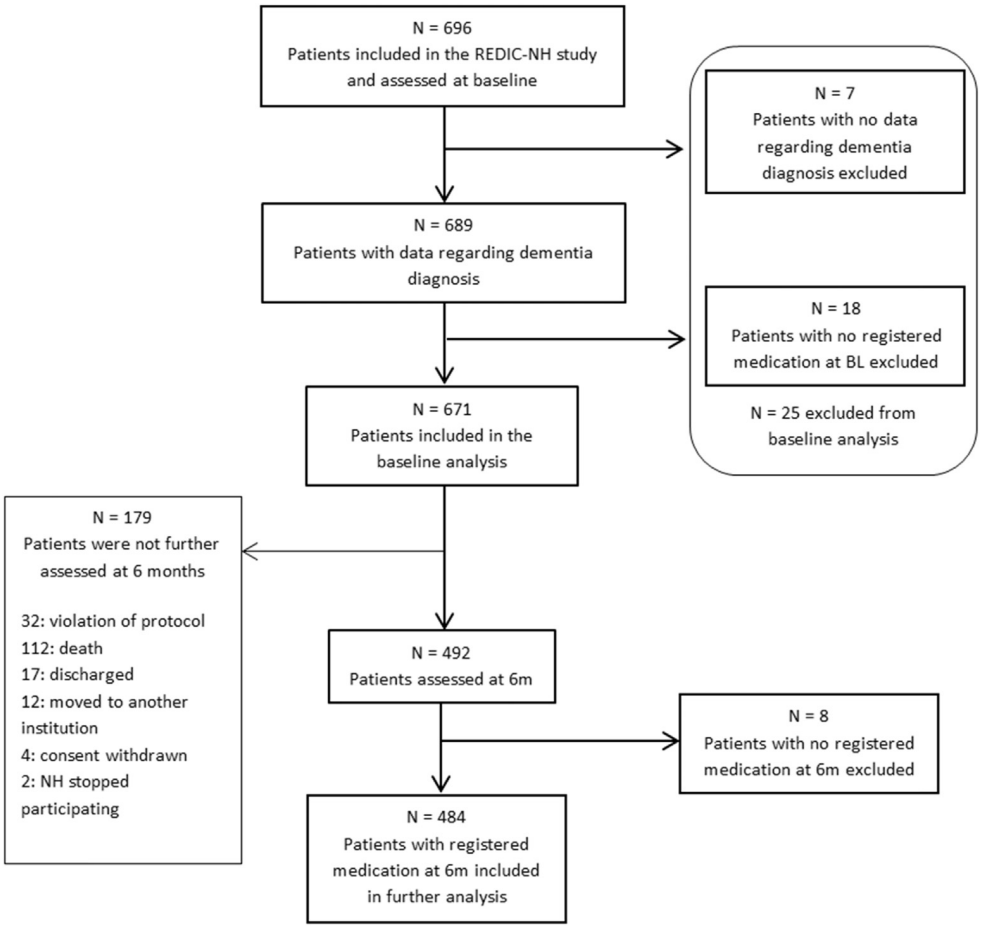

Fig. 1. Flow chart: Selection of patients for analysis.

Table 1
Validated Instruments Used to Collect Clinical Data

Clinical Feature	Structured Interview/Checklists/Other Methods	Ranging Score	Comments
Cognitive function	Mini-mental State Examination (MMSE)	0–30	A higher score indicates better cognitive function.
Neuropsychiatric symptoms	The Neuropsychiatric Inventory 12-item nursing home version (NPI-NH)*	0–12	Item score was calculated by multiplying severity (score 1–3) by frequency (score 1–4). An NPI-NH item score of 4 and above was considered clinically significant (CS-NPS).[20–22]
	The Cornell scale for depression in dementia (CSDD)	0–38	A higher score indicates more severe symptoms.[23]
Medication	The Anatomic Therapeutic Chemical (ATC) classification system		Psychotropic drugs were grouped as antipsychotics (N05A except lithium), antidepressants (N06A), anxiolytics (N05B), hypnotic/sedatives (N05C), and anti-dementia medication (N06D).†
Physical health status and pain	The General Medical Health Rating (GMHR) scale	Excellent, good, fair, poor	Used to assess the general medical health status of each participant.[24]
	The Charlson comorbidity index	Yes/No for each item	18 different The Charlson comorbidity index groups of diseases.[25]
	The Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID-2)	0–100	10 items, each ranging from 0–10. A higher score indicates more severe pain.[26]
Functioning in daily living and quality of life (QoL)	The Physical Self-Maintenance Scale (PSMS)	1–6	A higher score indicates a higher level of functioning.[27]
	The Quality of Life in Late-Stage Dementia scale (QUALID)	11–55	Proxy-based assessment scale, where lower scores indicate a higher QoL.[28,29]

*A previous principal component analysis identified the NPI-NH subsyndromes: NPI-NH agitation (agitation/aggression, disinhibition, and irritability), NPI-NH psychosis (delusions and hallucinations), and NPI-NH affective (depression and anxiety).[19,30]

†For each patient, we analyzed the exposure to a PTD group, but we did not take into consideration if a patient was prescribed 2 or more PTDs in the same group, except for antipsychotics.

remaining patients, 179 patients dropped out before 6m, and 484 patients were included in the analysis.

Seventy-four percent of data collectors were nurses who completed a 2-day training program. They were supervised by 10 research nurses, who completed a 5-day standardized training program. Information was collected using structured interviews with the patient, their next of kin and other caregivers, clinical examinations, and medical records.

Assessments Included in This Study

Age, gender, marital status, the type of NH unit, the number of patients living in each unit, and the number of health care providers working dayshift on a weekday per unit were collected. Cognitive function, NPS, medication, physical health status and comorbidity, pain, functioning in daily living, and quality of life (QoL) were collected using validated instruments as reported in Table 1.[20–30] Based on all collected information, mild cognitive impairment, dementia, and its etiological subtypes were diagnosed by the authors G.S. and S.B. according to *International Classification of Diseases, 10th Revision* (ICD-10) criteria.[19]

Statistics

IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY) and SAS Institute Inc. (Cary, NC) SAS version 9.4 statistical software were used for the analyses.

BL characteristics were analyzed in the whole cohort as well as stratified by dementia status. Continuous variables were presented as means and standard deviations (SD), and categorical variables as frequencies and percentages. Differences between dementia groups and between patients excluded and included in further analyses were assessed by a linear mixed model for continuous variables and generalized linear mixed model for categorical variables with random effects for NH units. For each PTD category, prevalence at BL and 6m, and incidence and persistence between BL and 6m were calculated. Prevalence was defined as the proportion of patients prescribed a particular PTD category. Incidence was defined as the proportion of patients prescribed a particular PTD category at 6m relative to the number of patients not prescribed the same PTD category at BL. Persistence was defined as the proportion of patients prescribed a particular PTD category at 6m relative to the number of patients prescribed the same PTD category at BL.

Change in the dichotomous outcome "PTD category use" (yes/no) was assessed with generalized linear models with fixed effects for time dummy (with BL as reference), dementia status at BL (with dementia as reference), and interaction between those 2 variables. The model contained random intercepts for patients nested within NH units. Predefined covariates, age, gender, marital status, physical health, functioning in daily living, cognitive function, depression, NPS (apathy and agitation, psychosis, and affective subsyndrome), Charlson Comorbidity Index, QoL, pain, type of unit, and number of staff members per unit working dayshift were then included in the models as fixed effects together with the interactions between each covariate and dementia status at BL. Akaike's Information Criteria (AIC, smaller values indicate a better model) was applied to reduce the multiple models for excessive interactions and covariates. Results were tabulated only for the interactions and covariates retained in the model.

Most of the covariates had missing values. For Mini-Mental State Examination, Physical Self-Maintenance Scale, QoL, and NPS scores, the missing values were imputed for each item separately by drawing a random number from its empirical distribution. Missing values for Charlson comorbidity index were substituted by zero. Only cases with fewer than 50% missing item values were imputed. The regression models were estimated for the cases with no missing values on covariates ($n = 402$). Those included in the regression analysis were compared with those not included ($n = 82$) by appropriate tests.

The results of the generalized linear mixed models were presented as odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). The level of significance was set at 5%.

Ethical and Legal Considerations

The patients' capacity to consent to participation in the study was evaluated by the NH personnel. A written consent for participation was signed. The participants' next of kin gave consent on behalf of those patients lacking the capacity to consent and for providing information about themselves. The Regional Ethics Committee for Medical Research in South-Eastern Norway approved the study (2011/1738).

Table 2
Demographic and Clinical Data of the Patients at Admission to the Nursing Homes (N = 671)

Variable	Total (N = 671)	Dementia (n = 563)	No Dementia (n = 108)	*P* Value*
Age				
Mean (SD)	84.4 (7.5)	84.1 (7.5)	86.4 (7.1)	**.021**
Gender				
Female, n (%)	432 (64.4)	365 (64.8)	67 (62.0)	.579
Marital status				
Not married, n (%)	459 (69.3)	376 (67.6)	83 (78.3)	
Married, partnership, n (%)	203 (30.7)	180 (32.4)	23 (21.7)	**.029**
GMHR				
Poor/Fair, n (%)	339 (52.6)	273 (50.6)	66 (62.9)	.093
Good/Excellent, n (%)	305 (47.4)	266 (49.4)	39 (37.1)	
Charlson comorbidity index	N = 608	n = 509	n = 99	
Mean (SD)	3.0 (2.3)	2.9 (2.1)	3.5 (2.9)	**.010**
PSMS	N = 669	n = 562	n = 107	
Mean (SD)	1.4 (1.3)	1.4 (1.3)	1.4 (1.3)	.389
MMSE	N = 590	n = 494	n = 96	
Mean (SD)	15.9 (6.3)	14.7 (5.6)	22.5 (5.6)	**<.001**
CSDD	N = 637	n = 533	n = 104	
Mean (SD)	6.4 (5.2)	6.6 (5.2)	5.8 (4.7)	.139
NPI total	N = 667	n = 560	n = 107	
Mean (SD)	14.2 (17.0)	15.2 (17.6)	9.2 (12.6)	**.001**
NPI-Agitation†	N = 650	n = 543	n = 107	
Mean (SD)	4.1 (7.0)	4.5 (7.3)	2.0 (4.8)	**.002**
NPI-Psychosis†	N = 649	n = 543	n = 106	
Mean (SD)	1.7 (4.0)	1.9 (4.2)	0.7 (2.3)	**.014**
NPI-Affective†	N = 661	n = 554	n = 107	
Mean (SD)	3.7 (5.8)	3.9 (5.9)	2.7 (4.5)	.052
NPI-Apathy	N = 659	n = 552	n = 107	
Mean (SD)	1.3 (2.8)	1.4 (2.8)	1.2 (2.8)	.434
QUALID	N = 667	n = 560	n = 107	
Mean (SD)	19.9 (7.2)	20.0 (7.2)	19.4 (7.0)	.325
Total prescribed drugs				
Mean (SD)	6.1 (3.1)	5.9 (3.0)	7.5 (3.5)	**<.001**
MOBID 2	N = 643	n = 538	n = 105	
Mean (SD)	2.1 (2.2)	2.0 (2.1)	2.9 (2.4)	**<.001**
Type of unit				
Regular unit	370 (55.1)	292 (51.9)	78 (72.2)	.985
Special care unit	216 (32.2)	207 (36.8)	9 (8.3)	
Respite and rehabilitation unit	85 (12.7)	64 (11.4)	21 (19.4)	
Number of patients per unit	N = 669	n = 561	n = 108	
Mean (SD)	12.0 (6.2)	11.5 (5.9)	14.7 (7.2)	.069
Number of staff members per unit working dayshift	N = 670	n = 562	n = 108	
Mean (SD)	3.7 (2.0)	3.6 (1.9)	4.2 (2.2)	.237

CSDD, Cornell scale for depression in dementia; GMHR, General Medical Health Rating Scale; MMSE, Mini-Mental Status Evaluation; MOBID-2 Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; NPI, The Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; QUALID, Quality of Life in Late-Stage Dementia.
P values < .05 (statistical significance) are reported in bold.

*Comparison between patients with dementia and patients with no dementia; *linear mixed model* is estimated for continuous variables and *generalized linear mixed model* for categorical variables. The models contain random *effect* for unit nested within NHs.

†NPI-subsyndromes are calculated as the sum of the following items: NPI-Agitation = Agitation + Disinhibition + Irritability, NPI-Psychosis = Delusions + Hallucinations, NPI-Affective = Depression + Anxiety.

Results

Table 2 presents the demographics and clinical data of the patients at admission to the NH. The mean (SD) age of the total sample (N = 671) was 84.4 (7.5) years, 64.4% were women, and 30.7% were married/in a partnership. Patients with dementia (83.9%) were younger ($P = .021$), scored lower on the Charlson comorbidity index ($P = .01$), and had less pain ($P < .001$) compared with patients without dementia, although there was no difference in the general physical health between the 2 groups assessed with the General Medical Health Rating scale. Patients with dementia had more severe NPS (NPI total score; $P = .001$) and had a higher score in the NPI-agitation subsyndrome ($P = .002$) and NPI-psychosis subsyndrome ($P = .014$). The patients were prescribed on average 6.1 drugs a day, but participants with dementia received fewer drugs (mean 5.9) compared with patients without dementia (mean 7.5, $P < .001$).

Patients excluded or dropped out (n = 187) had poorer general physical health, a higher level of depression, a lower QoL, and a lower level of functioning compared with those who remained in the study (Supplementary Material, Supplementary Table 1).

Table 3 presents the prevalence, incidence and persistence of PTD prescription in patients with dementia. We found an overall increase in the prescription of any PTD (BL: 67.5%, 6m: 74.0%; $P = .008$). There was a significant increase in the prescription rates of antidepressants (BL: 31.0%, 6m: 40.1%; $P < .001$), antipsychotics (BL: 13.5%, 6m: 19.0%; $P < .001$), anxiolytics (BL: 17.1%, 6m: 21.4%; $P = .004$), and sedatives/hypnotics (BL: 22.6%, 6m: 30.3%; $P < .001$) between BL and 6m. The persistence of prescription 6 months after NH admission was more than 60%, except for typical antipsychotics, in which the prescription was less persistent compared with atypical antipsychotics (41.7%/72.2%). The incidence of PTD prescription was highest for antidepressants (19.5%) and sedatives/hypnotics (16.8%).

Table 4 presents the results from the bivariate and multiple generalized linear mixed models assessing changes in prescription between BL and 6m, for all the major categories of PTDs.

In the bivariate model, we found that antidepressants were more likely to be prescribed at 6 months compared with BL in people both with (OR 7.3; 95% CI 2.8–18.9; $P < .001$) and without dementia (OR 10.5; 95% CI 1.3–86.1; $P = .028$) with no significant difference between

Table 3
Prevalence of Psychotropic Drug Prescription in Patients With Dementia at Baseline and 6 Months' Follow-Up; Persistence and Incidence of Psychotropic Drug Prescription in Patients With Dementia From BL to 6m, N = 416

Medication	Prevalence			Persistence[†]	Incidence[‡]
	BL	6m	*P* value[*]		
	n (%)	n (%)		n (%)	n (%)
Antidepressants	129 (31.0)	167 (40.1)	<**.001**	111/129 (86.0)	56/287 (19.5)
Typical antipsychotics	24 (5.8)	20 (4.8)	.220	10/24 (41.7)	10/392 (2.6)
Atypical antipsychotics	33 (7.9)	60 (14.4)	<**.001**	24/33 (72.7)	36/383 (9.4)
Any antipsychotic	56 (13.5)	79 (19.0)	<**.001**	39/56 (69.6)	40/360 (11.1)
Anxiolytics	71 (17.1)	89 (21.4)	**.004**	46/71 (64.8)	43/345 (12.5)
Sedatives/hypnotics	94 (22.6)	126 (30.3)	<**.001**	72/94 (76.6)	54/322 (16.8)
Anti-dementia drugs	128 (30.8)	122 (29.3)	.349	90/128 (70.3)	32/288 (11.1)
Any psychotropic drug	281 (67.5)	308 (74.0)	.008		
	Mean (SD)	Mean (SD)			
Total medication[§]	5.8 (3.0)	6.5 (2.8)	<**.001**		

P values < .05 (statistical significance) are reported in bold.
[*]Comparison between the prescription of a psychotropic drug at baseline and 6 months follow-up; *linear mixed model* is estimated for continuous variable and *generalized linear mixed model* for categorical variables.
[†]Persistence is the proportion of patients exposed to a PTD category at 6m relative to the number of patients who were prescribed the same PTD category at BL.
[‡]Incidence is the proportion of patients exposed to a PTD category at 6m relative to the number of patients who were not prescribed the same PTD category at BL.
[§]Any type of medication registered with ATC-number.

the groups. In the multiple model, we found that younger patients and those with higher NPS-affective subsyndrome score had higher odds of receiving antidepressants (OR 1.4; 95% CI 1.2–1.7; $P < .001$).

Three interactions were identified in the multiple model. Men with dementia had higher odds of being prescribed antidepressants than men without dementia at both assessment points. There were no

Table 4
Bivariate and Multiple Models of the Logistic Regression Analysis Regarding Changes in Prescription Between BL and 6m, for all the Major Categories of Psychotropic Drugs

	Antidepressants		Antipsychotics		Anxiolytics		Sedatives and Hypnotics	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Bivariate models, N = 402								
6m vs. BL								
No dementia	10.5 (1.3–86.1)	**.028**	3.1 (0.1–69.4)	.468	14.5 (1.1–193.7)	**.043**	2.4 (0.6–9.1)	.201
Dementia	7.3 (2.8–18.9)	<**.001**	3.4 (1.3–8.7)	**.012**	2.1 (1.0–4.7)	.060	4.6 (1.7–12.8)	**.003**
Dementia vs. No dementia	0.7 (0.1–6.4)	.749	1.1 (0.0–26.9)	.965	0.1 (0.0–2.1)	.160	1.9 (0.4–9.9)	.428
Multiple models, N = 402								
6m vs. BL								
No dementia	5.7 (1.1–28.5)	**.034**			12.7 (1.1–153.3)	**.045**	2.4 (0.7–8.4)	.173
Dementia	3.0 (1.6–5.6)	**.001**			2.1 (1.0–4.5)	.064	3.9 (1.6–9.1)	**.002**
Dementia vs. No dementia	0.5 (0.1–2.8)	.443			0.2 (0.0–2.1)	.169	1.6 (0.4–7.4)	.539
Age	0.9 (0.8–1.0)	**.005**						
No dementia								
Dementia								
Dementia vs. No dementia								
Women								
Dementia vs. No dementia								
BL	0.2 (0.01–6.5)	.389					0 (0–0.2)	**.016**
6m	0.1 (0.004–3.4)	.216					0 (0–0.2)	**.018**
Men								
Dementia vs. No dementia								
BL	2206.0 (4.1–>999)	**.016**					0.3 (0–299.4)	.705
6m	1150.0 (2.6–>999)	**.023**					0.4 (0–450.7)	.803
Men vs. Women								
No dementia	0.0001 (0–0.02)	**.001**					0.0003 (0.0–1.3)	.058
Dementia	0.6 (0.1–2.2)	.391					1.4 (0.4–5.5)	.599
Dementia vs. No dementia	0.0001 (0–0.04)	**.003**					0.0002 (0.0–1.03)	.052
Charlson comorbidity index								
No dementia	1.7 (0.9–3.2)	.093						
Dementia	0.9 (0.7–1.3)	.577						
Dementia vs. No dementia	0.5 (0.3–1.1)	.083						
NPI-Agitation[*]								
No dementia							0.5 (0.2–1.1)	.096
Dementia							1.0 (0.9–1.2)	.546
Dementia vs. No dementia							2.2 (0.9–5.4)	.083
NPI-Psychosis[*]								
No dementia	0.4 (0.2–1.0)	**.042**						
Dementia	1.0 (0.9–1.2)	.843						
Dementia vs. No dementia	2.4 (1.0–5.8)	**.048**						
NPI-Affective[*]	1.4 (1.2–1.7)	<**.001**			1.1 (1.0–1.3)	.083	1.2 (1.1–1.5)	**.013**

P values < .05 (statistical significance) are reported in bold.
[*]NPI, The Neuropsychiatric Inventory; NPI-subsyndromes are calculated as the sum the following items: NPI-Agitation = Agitation + Disinhibition + Irritability, NPI-Psychosis = Delusions + Hallucinations, NPI-Affective = Depression + Anxiety.

significant differences among women. The association between dementia and prescription of antidepressants was significantly different between men and women ($P = .003$ for interaction). Overall, the association between the prescription of antidepressants and NPI-psychosis was significantly different between patients with and without dementia ($P = .048$ for interaction), whereas the difference was not significant for Charlson comorbidity index. However, with increasing comorbidity, patients with dementia were prescribed significantly fewer antidepressants than patients without dementia at both BL and 6m (for Charlson comorbidity index ≥ 2).

In the bivariate model, antipsychotics were more likely to be prescribed at 6m than at BL among patients with dementia (OR 3.4; 95% CI 1.3–8.7; $P = .012$), with no significant change among those without dementia. This association, however, did not differ significantly between diagnosis groups. The prevalence of antipsychotic prescription among people without dementia was too low to allow for multiple model estimation.

In the bivariate model, we found no difference in anxiolytic prescription rates between BL and 6m in patients with dementia, whereas patients without dementia were prescribed slightly more anxiolytics at 6m compared with BL (OR 14.5; 95% CI 1.1–193.7; $P = .043$) with no significant differences between diagnosis groups regarding this association. In the multiple model, we found no significant associations.

In the bivariate model, we found that sedatives were more likely to be prescribed at 6m compared with BL in patients with dementia than in patients without dementia (OR 4.6; 95% CI 1.7–12.8; $P = .003$), although overall, this association did not differ significantly between the diagnosis groups. In the multiple model, more severe affective symptoms were associated with a higher sedative prescription rate (OR 1.2; 95% CI 1.1–1.5; $P = .013$). Even though not significant, 2 interactions were retained in the model. People with dementia were prescribed more sedatives at 6m than BL (OR 3.9; 95% CI 1.6–9.1; $P = .002$), with no gender differences. Further, among people with dementia, a higher NPI-agitation score was associated with an increased odds of sedatives prescription at 6m compared with BL, whereas among patients without dementia, there was no difference between the 2 assessment points. We found that the differences between patients with and without dementia regarding the odds of sedative prescription were significant only for NPI-agitation subsyndrome scores below 5 at BL and below 4 at 6m.

Compared with the excluded cases from the regression analysis, the included cases had a significantly higher level of functioning ($P = .004$); lived more often in regular units ($P = .001$) and in wards with a higher number of patients per unit ($P = .001$); and had a significantly lower NPI total score ($P = .009$), NPI-agitation subsyndrome score ($P = .013$), and QoL ($P = .005$) (Supplementary Material, Supplementary Table 2).

Discussion

Prescription rates of antidepressants, antipsychotics, anxiolytics, sedatives, and hypnotics increased in people with dementia during the first 6 months after admission, with a very high persistence of prescription of any PTD category.

Antidepressants

Thirty-one percent of the patients with dementia were prescribed antidepressants at admission, increasing to 40.1% 6 months later. Comparable results can be found in a Norwegian study,[31] and in international studies, although their results do not differentiate between people with and without dementia.[17,32,33] A Norwegian longitudinal study showed that antidepressant prescription rates increased after NH admission, supporting our findings.[34]

Higher NPI-affective subsyndrome scores and younger age at admission were associated with higher odds of antidepressant prescription at both assessment points, comparable to previous international studies,[12,13] although their cross-sectional nature makes it difficult to compare with the results from our study.

Compared with people without dementia, patients with dementia had higher odds of being prescribed antidepressants with increasing NPI-psychosis subsyndrome score. This finding is difficult to explain, considering there is little evidence of effectiveness in the use of antidepressants to treat psychosis in dementia.[35] On the other hand, antidepressants in this case might be prescribed to control concurrent symptoms to psychosis, such anxiety or agitation.

Higher comorbidity at admission had lower odds of antidepressant prescription at both assessment points. Physicians might avoid prescribing antidepressants due to adverse effects and interactions in patients with several illnesses. When depression is comorbid to other diseases, the physical health has a greater decline.[36] It is therefore important to identify patients with a higher comorbidity and depression and treat them correctly. Undetected depression in older institutionalized people is still common,[37] and almost half of patients with depression do not receive adequate treatment.[31] A meta-analysis showed low evidence for effectiveness of antidepressant use in people with Alzheimer's disease,[7] and national guidelines suggest the use of antidepressants as first-line treatment only for moderate to severe depressive symptoms in patients with dementia.[38] It is alarming that there is a high prevalence of antidepressants prescription among older people in NHs, considering their potentially increased risk of adverse effects.[39]

Antipsychotics

At admission, 13.5% of the patients with dementia received antipsychotics, increasing to 19% 6 months later. Most were atypical antipsychotics. International studies showed higher prevalence rates of antipsychotics use at NH admission: in Canada 27.2%, in Belgium 28.5%, and in Australia 27.1%.[14,17,32] The lower prevalence reported in Norway might be explained by the increasing awareness of the adverse effects antipsychotics may cause in people with dementia, and the national and local campaigns to find alternative nonpharmacological approaches.

Antipsychotics are often used in NHs to treat NPS. National guidelines warn that antipsychotics should be prescribed for short periods of time, and only in severe cases of agitation and aggression.[38] Unfortunately, antipsychotic use is still persistent over time in institutionalized older patients, although the prevalence results we found are considerably lower than another Norwegian study conducted in NHs[6]; however, a recent Norwegian study showed a considerable decrease in the prescription of antipsychotic drugs between 2004 and 2011 (more than a 30% reduction in use), with only minor changes for the other PTD.[15] A Norwegian study showed that the prevalence of NPS is high from admission to a NH over time, and the mean NPI-agitation subsyndrome score tends to increase.[18] This might explain the increase of antipsychotic prescription during the first 6 months in our study, as physicians tend to treat NPS with antipsychotics. It is still alarming that antipsychotics are used in patients with dementia, considering that antipsychotic review and reduction in antipsychotic use, together with the implementation of nonpharmacological treatments such as social interaction, decreases the risk of mortality.[40]

Sedatives/Hypnotics and Anxiolytics

The prevalence of anxiolytic prescription was 17.1% at admission and 21.4% 6 months later, but with no significant differences between the 2 assessment points. In patients with dementia, 22.6% were prescribed sedatives at admission and 30.3% 6 months later. Comparable

results for sedatives prescription ranged from 23.8% to 35.2% in Norwegian studies.[6,41,42] International studies showed varying prevalence results: in Belgium 43.3%, in Canada 17.3%, in Australia 4.8%, and 28.1% to 33.4% in France.[14,17,32,33]

The prescription of sedatives and hypnotics increased significantly during the first 6 months after NH admission; however, other studies showed differing results: in Belgium rates decreased from 43.0% to 41.5% 2 years after admission,[32] whereas in Australia rates increased from 4.8% to 6.0% 6 months after admission.[17] These differences should be interpreted cautiously due to the different research populations and study methods.

We found that patients with more affective symptoms at admission were at a higher risk of sedative and hypnotic prescription at both assessment points. This differs from results presented by Zuidema et al.,[12] in which hypnotic use was not associated with affective NPS. Affective symptoms such as depression and anxiety are common and persistent in NHs,[18] but may decrease over time.[5,43] Our findings might be explained by the fact that sedatives and hypnotics are usually prescribed to treat depressive symptoms such as sleep disturbances or anxiety at night. Unfortunately, sedatives or hypnotics are still among the most commonly used drugs in people with dementia,[44] despite the large consensus on the fact that these drugs should be used for as short a time as possible as an adjunct to other nonpharmacological treatments.[45] The vast and persistent use of hypnotics in NHs and its increase should raise concern considering the amount of adverse effects hypnotics have on older individuals.[46]

Strengths and Limitations

This study is one of a few studies reporting data about PTD prescription in patients newly admitted to a NH and following up after admission together with changes in clinical factors. Previous studies reporting PTD use have been either cross-sectional or longitudinal with the registration of PTD use every 12 to 18 months. Assessing patients more frequently than every 12 to 18 months better identifies changes in a patient's medication over time.

This study has some limitations. The data collection was conducted by personnel in all the participating NHs, and that might give variability in the quality of the collected data; however, all data collectors had extensive training and supervision throughout the study period. We were not able to analyze data concerning daily dosage of PTD due to the high imprecision of the reported dosages. Even small changes in the PTD dosage might significantly influence a patient's clinical symptoms. Further, it was not possible to get information about patients who were prescribed no drugs versus patients in whom medication data were missing due to lack of precision in data collection, but not many patients were excluded for this reason. In addition, several reasons might have reduced the representativeness of the patients at admission to NHs: respite patients were excluded, and many patients who were eligible for inclusion did not participate in the study.[19] In addition, two-fifths of the included patients had to be excluded from the multiple model analysis due to missing values on covariates.

Conclusion and Implications

The prevalence and persistence of prescription of PTD at admission to Norwegian NHs is high, especially for antidepressants and sedatives/hypnotics. PTD prescription rates increased for all the major classes of PTDs from admission to 6 months. Although some treatment might be justified by the severity of NPS, medication appropriateness should be carefully evaluated right after NH admission to avoid unnecessary prescriptions. Frequent NPS evaluation might be useful to target deprescribing or continuation strategies and optimize PTD prescriptions.

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Supplementary Material

Supplementary Table 1
Comparison Between 484 Patients Who Were Included in the Analysis and 187 Patients Who Were Excluded/Dropped Out (N = 671)

Variable	Excluded (n = 187)	Included in Analysis (n = 484)	*P* Value*
Age			
Mean (SD)	85.1 (7.7)	84.1 (7.4)	.114
Gender			
Female, n (%)	112 (59.9)	320 (66.1)	.132
Marital status	n = 184	n = 478	
Not married, n (%)	124 (67.4)	335 (70.1)	
Married, partnership, n (%)	60 (32.6)	143 (29.9)	.555
GMHR	n = 175	n = 469	
Poor/Fair, n (%)	110 (62.9)	229 (48.8)	
God/Excellent, n (%)	65 (37.1)	240 (51.2)	**.002**
Charlson comorbidity index	n = 162	n = 446	
Mean (SD)	3.5 (2.4)	2.8 (2.2)	**.002**
PSMS	n = 185		
Mean (SD)	1.1 (1.2)	1.6 (1.3)	<**.001**
MMSE	n = 147	n = 443	
Mean (SD)	15.8 (6.5)	16.0 (6.2)	.928
CSDD	n = 171	n = 466	
Mean (SD)	7.1 (5.4)	6.2 (5.0)	**.036**
NPI total	n = 184	n = 483	
Mean (SD)	15.6 (17.6)	13.7 (16.8)	.103
NPI-Agitation†	n = 179	n = 471	
Mean (SD)	4.7 (7.9)	3.8 (6.7)	.055
NPI-Psychosis†	n = 174	n = 475	
Mean (SD)	1.3 (3.6)	1.9 (4.1)	.105
NPI-Affective†	n = 180	n = 481	
Mean (SD)	3.9 (6.0)	3.6 (5.7)	.411
NPI-Apathy	n = 180	n = 479	
Mean (SD)	1.6 (3.0)	1.3 (2.7)	.140
QUALID	n = 184	n = 483	
Mean (SD)	21.0 (7.6)	19.5 (6.9)	**.010**
Total prescribed drugs			
Mean (SD)	6.4 (3.2)	6.0 (3.1)	.149
MOBID 2	n = 170	n = 473	
Mean (SD)	2.4 (2.3)	2.0 (2.1)	.107
Type of unit			
Regular unit	98 (52.4)	272 (56.2)	.871
Special care unit	61 (32.6)	155 (32.0)	
Respite and rehabilitation unit	28 (15.0)	57 (11.8)	
Number of patients per unit		n = 482	
Mean (SD)	12.6 (6.7)	11.8 (6.0)	.281
Number of staff members per unit working dayshift		n = 483	
Mean (SD)	3.8 (2.1)	3.7 (1.9)	.534

CSDD, Cornell scale for depression in dementia; GMHR, General Medical Health Rating Scale; MMSE, Mini-Mental Status Evaluation; MOBID-2 Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; NPI, The Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; QUALID, Quality of Life in Late-Stage Dementia.
P values < .05 (statistical significance) are reported in bold.

*Comparison between patients included and excluded from the study; *linear mixed model* is estimated for continuous variables and *generalized linear mixed model* for categorical variables. The models contain random *effect* for unit nested within NHs.

†NPI-subsyndromes are calculated as the sum of the following items: NPI-Agitation = Agitation + Disinhibition + Irritability, NPI-Psychosis = Delusions + Hallucinations, NPI-Affective = Depression + Anxiety.

Supplementary Table 2
Comparison Between 402 Patients Who Were Included in the Analysis and 82 Patients Who Were Excluded/Dropped Out (N = 484)

Variable	Included in Analysis (n = 402)	Excluded From Analysis (n = 82)	*P* Value*
Age			
Mean (SD)	84.5 (7.2)	82.6 (8.4)	.059
Gender			
Female, n (%)	265 (65.9)	55 (67.1)	.841
Marital status	n = 402	n = 76	
Not married, n (%)	288 (71.6)	47 (61.8)	
Married, partnership, n (%)	114 (28.4)	29 (38.2)	.087
GMHR	n = 402	n = 67	
Poor/Fair, n (%)	202 (50.2)	27 (40.3)	
God/Excellent, n (%)	200 (49.8)	40 (59.7)	.131
Charlson comorbidity index	n = 402	n = 48	
Mean (SD)	2.8 (2.2)	2.6 (1.9)	.533
PSMS	n = 402	n = 82	
Mean (SD)	1.7 (1.3)	1.2 (1.1)	**.004**
MMSE	n = 402	n = 45	
Mean (SD)	16.2 (6.1)	15.1 (6.6)	.241
CSDD	n = 391	n = 75	
Mean (SD)	6.1 (5.0)	6.9 (5.3)	.187
NPI total	n = 402	n = 78	
Mean (SD)	12.8 (16.1)	19.1 (19.5)	**.009**
NPI-Agitation†	n = 402	n = 82	
Mean (SD)	3.4 (6.1)	6.0 (8.9)	**.013**
NPI-Psychosis†	n = 402	n = 78	
Mean (SD)	1.7 (4.0)	2.4 (4.3)	.190
NPI-Affective†	n = 402	n = 81	
Mean (SD)	3.5 (5.5)	4.3 (6.4)	.246
NPI-Apathy	n = 402	n = 78	
Mean (SD)	1.3 (2.7)	1.2 (2.5)	.814
QUALID	n = 402	n = 81	
Mean (SD)	19.1 (6.6)	21.8 (8.0)	**.005**
Total prescribed drugs	n = 402	n = 82	
Mean (SD)	6.1 (3.1)	5.7 (2.8)	.263
MOBID 2	n = 402	n = 82	
Mean (SD)	2.0 (2.1)	2.3 (2.2)	.309
Type of unit	n = 402	n = 82	
Regular unit	235 (58.5)	37 (45.1)	**.001**
Special care unit	115 (28.6)	40 (48.8)	
Respite and rehabilitation unit	52 (12.9)	5 (6.1)	
Number of patients per unit	n = 400	n = 82	
Mean (SD)	12.1 (6.1)	10.1 (4.9)	**.001**
Number of staff members per unit working dayshift	n = 402	n = 81	
Mean (SD)	3.7 (1.9)	3.4 (2.0)	.156

CSDD, Cornell scale for depression in dementia; GMHR, General Medical Health Rating Scale; MMSE, Mini-Mental Status Evaluation; MOBID-2 Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale; NPI, The Neuropsychiatric Inventory; PSMS, Physical Self-Maintenance Scale; QUALID, Quality of Life in Late-Stage Dementia.
P values < .05 (statistical significance) are reported in bold.

*Comparison between patients included and excluded from the study; *linear mixed model* is estimated for continuous variables and *generalized linear mixed model* for categorical variables. The models contain random *effect* for unit nested within NHs.

†NPI-subsyndromes are calculated as the sum of the following items: NPI-Agitation = Agitation + Disinhibition + Irritability, NPI-Psychosis = Delusions + Hallucinations, NPI-Affective = Depression + Anxiety.

II

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RESEARCH Open Access

Do prescription rates of psychotropic drugs change over three years from nursing home admission?

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Abstract

Background: In this longitudinal study, we describe how psychotropic drugs (PTDs) are prescribed in nursing home (NH) patients from admission and over a 3-year period, to understand which clinical and environmental factors are associated with PTD prescription.

Methods: We used data from the Resource Use and Disease Course in Dementia – Nursing Home (REDIC-NH) study, examining physical and mental health, dementia, and PTD prescription during a 3-year period from admission to a NH. Data were collected every six months. At baseline, we included 696 participants from 47 Norwegian NHs. We presented prevalence, incidence, and deprescribing rates of PTD prescriptions for each assessment point. We calculated the odds of receiving PTDs and used a generalized linear mixed model to analyze the variables associated with a change in odds throughout the 3-year period.

Results: PTD prescriptions were frequent throughout the 3-year period. Antidepressants had the highest prescription rates (28.4%–42.2%). Every PTD category had the highest incidence rate between admission and six months, and antipsychotics had the highest values (49.4%). Deprescribing rates were comparable between assessment points. The odds of antipsychotic prescriptions were lower for older people (OR = 0.96, 95%CI:0.92–0.99, $p = 0.023$). People with more severe dementia had lower odds of being prescribed sedatives/hypnotics (OR = 0.89, 95%CI:0.85–0.94, $p < 0.001$).

Conclusions: PTDs, particularly antidepressants, are widely prescribed over time to NH patients. Older patients are less likely to receive antipsychotics. A higher severity of dementia decreases the odds of being prescribed sedatives/hypnotics. Close attention should be paid to PTD prescriptions during long-term NH stay to avoid prolonged and excessive treatment with these types of drugs.

Trial registration: ClinicalTrials.gov Identifier: NCT01920100.

Keywords: Geriatric pharmacotherapy, Psychotropic drugs, Nursing homes

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Background

Up to 84.3% of nursing home (NH) residents have dementia [1]. During the course of their NH stay, they often experience neuropsychiatric symptoms (NPS), in particular irritability, depression, and anxiety [2]. NPS are usually targeted with both pharmacological and non-pharmacological measures, where the latter is still considered first-line treatment [3].

Psychotropic drugs (PTDs) such as antidepressants, antipsychotics, and sedatives/hypnotics are primarily prescribed to treat psychiatric disorders, but are often prescribed in NH patients to treat NPS [4], despite recent Norwegian guidelines recommend to be cautious while prescribing these drugs [5]. In people with dementia, antidepressants are not very effective at treating depression [6], and atypical antipsychotics have a negligible effect on agitation and psychosis [7]. Non-patient related factors can also influence PTD prescriptions, such as staff-patient ratio and staff distress related to patients' symptoms [8, 9], the knowledge gap among NH personnel about the related adverse effects of medication [10], communication education [11], and health care personnel's positive belief or confidence in prescribing or discontinuing medication [12, 13]. Moreover, it can be challenging to monitor a drug therapy, as different screening tools for inappropriate prescribing may recommend different pharmacological measures [14].

The use of PTDs in older adults leads to a series of potential adverse effects that can worsen their physical and cognitive function [15]. Commonly-known adverse effects associated with short- or long-term PTD use, such as akathisia, agitation, aggression, and anxiety, can mislead the caregiver to think that NPS are worsening, leading to a further increase in PTD dosages [16]. In addition, up to 86% of NH residents are exposed to polypharmacy (≥5 concomitant drugs) [17], increasing the risk of several adverse effects, morbidity, mortality, as well as inappropriate prescribing [18].

Detecting an inappropriate therapy at an early stage of NH stay might help physicians avoid later complications. A vast body of literature describes PTD prescriptions in NHs. Most of the studies have a cross-sectional nature and vary in their methodological approaches, which makes it challenging to compare results [8, 19–21]. The longitudinal aspects of PTD prescriptions are important in order to find possible explanations behind treatment decisions over time. A recent study has shown frequent and persistent use of PTDs in Norwegian NHs during a 72-months follow-up [22]. The assessment of patients from admission is also particularly relevant, as NH transitions may worsen the residents' psychiatric symptoms and their perceived quality of life [23], possibly leading physicians to initiate a pharmacological treatment during this transition. Very few longitudinal studies have described PTD prescription rates in NH residents from admission [24–26], and even fewer have described PTD prescriptions in relation to physical, cognitive, psychological, and environmental factors [27, 28]. None have presented a comprehensive analysis of systematic clinical factors, NPS, and environmental factors and their association with PTD prescriptions.

A recent study based on the same data material used in this paper has explored which clinical factors at admission could predict changes in PTD prescriptions six months after NH admission [29]. Besides a general increase in prescription of all the major PTDs during the first six months, higher affective subsyndrome scores for the Neuropsychiatric Inventory 12-item nursing home version (NPI-NH) were associated with a higher odds of prescribing antidepressants, sedatives, and hypnotics at admission and six months later [29, 30].

The aim of this paper is to investigate the course of PTD prescription in NH patients, focusing on prevalence, incidence and deprescribing rates, and their relationship to clinical and environmental factors, during a three-year follow-up from admission to NHs.

Methods

We used data from the Resource Use and Disease Course in Dementia - Nursing Home (REDIC-NH) study, designed to follow NH residents from admission until death [31]. At baseline (BL), 696 patients admitted to 47 Norwegian NHs were included.

Among 47 recruited NHs, only 38 NHs collected information (gender and age) on eligible patients not included in the study. As described by Røen et al. (2017), in these 38 NHs 1331 patients were eligible for inclusion, 724 patients were excluded, and 607 were included [31]. For the remaining nine NHs, we do not, unfortunately, have information about not-inclusion, but the nine NHs included 89 patients giving a total of 696 included patients in the study. The NHs, representing small and large facilities, were situated in urban and rural areas in four Norwegian counties [31]. BL assessments were registered between March 2012 and November 2014, and the participants were further assessed every six months until death or until 3-year NH-stay. To be included at BL, patients had to be at least 65 years old or younger than 65 years with established dementia, had to have a life expectancy > 6 weeks and an expected NH stay of > 4 weeks. The flow chart for the sample inclusion, together with attrition causes between each assessment point, are presented in Fig. 1.

Demographic data were registered at BL. Dementia at BL was diagnosed by SB and GS according to ICD-10 criteria, based on all collected data. At each assessment point, NH characteristics and daily medication use according to the ATC system were registered. Data

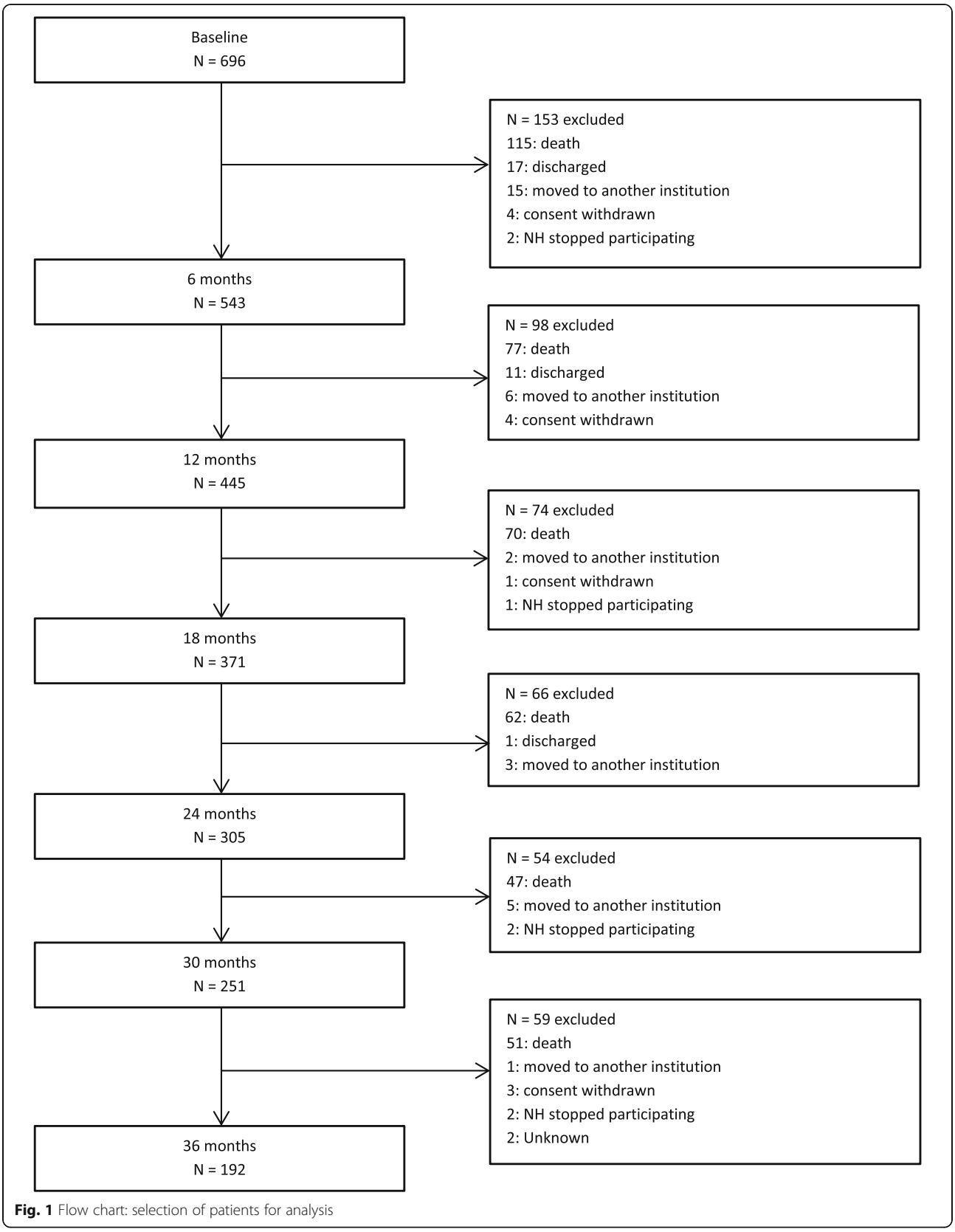

Fig. 1 Flow chart: selection of patients for analysis

regarding medication "as needed" was not recorded. PTDs were grouped as follow: antidepressants (N06A), antipsychotics (N05A, consisting of typical and atypical antipsychotics, except lithium), anxiolytics (N05B), sedatives and hypnotics (N05C), and antidementia drugs (N06D, consisting of cholinesterase inhibitors and memantine). Validated instruments were used to assess dementia severity (the Clinical Dementia Rating (CDR) scale) [32], level of functioning (the Physical Self-Maintenance Scale - PSMS) [33], NPS (the Neuropsychiatric Inventory 12-item nursing home version – NPI-NH - and the Cornell Scale for Depression in Dementia - CSDD) [30, 34], physical function (the General Medical Health Rating (GMHR) scale and the Charlson Comorbidity Index) [35, 36], and quality of life (the Quality of Life (QoL) in Late-Stage Dementia (QUALID) scale) [37].

Statistical analyses

Demographic, clinical, and environmental characteristics at BL are presented as means and standard deviations (SDs) for continuous variables, and frequencies and percentages for categorical variables. We calculated the prevalence, incidence rate and deprescribing rate of prescription for any PTD as well as for each PTD subgroup (antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics, and antidementia drugs). We defined prevalence as the proportion of patients prescribed a particular PTD at each assessment point. Incidence rate / deprescribing rate was defined as the proportion of patients prescribed / deprescribed a particular PTD at one assessment point relative to the number of patients not prescribed / prescribed the same PTD at the previous assessment point. We present the total number of medications and the total number of PTDs as mean and SD, the numbers for the whole cohort, as well as stratified by dementia diagnosis.

We estimated an unadjusted generalized linear mixed model with second-order time component to assess a possible non-linear trend in odds for use of antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics, and antidementia drugs. Pre-chosen covariates assessed at baseline or simultaneously with drug use covariates, one at a time, were included into the model as additional fixed effects together with the interaction term between the covariate and time. Finally, we estimated an adjusted model with time, all covariates and interactions included. We applied Bayesian Information Criterion (smaller values means better model) to eliminate excessive interactions. A significant interaction implies that a covariate is significantly associated with change in odds over time. All models included random effects for patients nested within NHs. The unadjusted time trend is illustrated graphically as odds of being prescribed a particular PTD at each assessment point with 95% confidence intervals (CI). The associations between covariates and prescription of a particular PTD were tabulated as odds ratios (OR) and 95% CI whenever interaction was absent. Regression coefficients and standard errors (SEs) are presented for covariates included in the interactions. For easier interpretation, these results are also illustrated graphically. All tests were two-sided and results with p-values ≤0.05 were considered statistically significant.

Most covariates had some missing values. For cases with fewer than 50% missing values on items of a particular scale (CDR, CSDD, PSMS, QoL, and NPS scores), we imputed missing values for each item separately by drawing a random number from its empirical distribution. For the Charlson Comorbidity Index, we substituted missing values with zero.

We used IBM® SPSS® Statistics version 26® and SAS Institute Inc.® SAS® version 9.4 statistical software for the analyses.

Results

At BL, 696 patients were included. The majority had dementia (83.8%), were female (64.1%), had a fair/poor physical health (52.4%), and lived in a regular NH unit (55.3%) (Table 1).

Prevalence, incidence and deprescribing rates for the major PTD categories are presented Table 2. Selected results are illustrated in Figs. 2 and 3.

According to unadjusted generalized linear mixed models, there was a significant non-linear time trend in odds of prescribing antidepressants and anxiolytics, but not for antipsychotics, sedatives and hypnotics, or antidementia drugs (Fig. 4).

Table 3 presents the results of adjusted generalized linear mixed models. Time trend in odds of prescribing certain PTDs remained nearly unchanged after adjustment for covariates. None of the covariates were associated with *change* in odds over time for the five assessed PTD categories (non-significant interactions between covariates and time), except for CSDD, which was significantly associated with change in odds of prescribing sedatives and hypnotics. For CSDD scores < 8, the change in odds of prescribing sedatives and hypnotics was not significantly associated with CSDD. For CSDD scores > 8, the increasing CSDD score was associated with higher odds of prescribing sedatives and hypnotics from BL to 18m, and decreased odds of prescribing sedatives and hypnotics from 18m to 36m (Fig. 5).

Higher scores of CDR sum of boxes were associated with lower odds of prescribing sedatives and hypnotics (OR = 0.89, 95%CI:0.85–0.94, $p < 0.001$).

Being female, higher CSDD score, and NPI-affective subsyndrome score were significantly associated with higher odds of prescribing antidepressants (OR = 2.09,

Table 1 Demographic and clinical data of patients at nursing home admission, *N* = 696

Variable	No dementia *N* = 113	Dementia *N* = 583	Total *N* = 696
Age			
N	113	580	693
Mean (SD)	86.4 (7.0)	84.0 (7.5)	84.4 (7.5)
Gender, female			
n/N (%)	70/113 (61.9)	376/583 (64.5)	446/696 (64.1)
GMHR			
Poor/Fair, n/N (%)	69/109 (63.3)	280/557 (50.3)	349/666 (52.4)
Good/Excellent, n/N (%)	40/109 (36.7)	277/557 (49.7)	317/666 (47.6)
Charlson Comorbidity Index			
N	104	525	629
Mean (SD)	3.5 (2.8)	2.8 (2.1)	2.9 (2.3)
PSMS			
N	112	582	694
Mean (SD)	1.5 (1.3)	1.5 (1.3)	1.5 (1.3)
MMSE			
N	104	516	620
Mean (SD)	22.5 (5.6)	14.8 (5.5)	16.1 (6.2)
CDR sum of boxes			
N	111	578	689
Mean (SD)	5.3 (4.2)	11.3 (3.6)	10.3 (4.3)
CSDD			
N	109	551	660
Mean (SD)	5.7 (4.7)	6.7 (5.3)	6.5 (5.2)
NPI total			
N	112	573	685
Mean (SD)	9.2 (12.5)	15.4 (17.5)	14.4 (17.0)
NPI-agitation[a]			
N	112	580	692
Mean (SD)	2.0 (4.8)	4.5 (7.3)	4.1 (7.0)
NPI-psychosis[a]			
N	112	570	682
Mean (SD)	0.7 (2.3)	1.9 (4.2)	1.7 (4.0)
NPI-affective[a]			
N	112	577	689
Mean (SD)	2.8 (4.6)	3.9 (5.9)	3.7 (5.7)
NPI-caregivers			
N	112	581	693
Mean (SD)	3.4 (5.0)	6.0 (7.4)	5.5 (7.2)
NPI-apathy			
N	112	574	686
Mean (SD)	1.1 (2.7)	1.4 (2.8)	1.3 (2.8)
QUALID			
N	112	580	692

Table 1 Demographic and clinical data of patients at nursing home admission, *N* = 696 *(Continued)*

Variable	No dementia *N* = 113	Dementia *N* = 583	Total *N* = 696
Mean (SD)	19.3 (6.9)	20.0 (7.2)	19.9 (7.2)
MOBID-II			
N	110	557	667
Mean (SD)	2.8 (2.4)	2.0 (2.1)	2.1 (2.1)
Type of unit			
Regular unit, n/N (%)	82/113 (72.6)	303/583 (52.0)	385/696 (55.3)
Special care unit, n/N (%)	10/113 (8.8)	216/583 (37.0)	226/696 (32.5)
Respite and rehabilitation unit, n/N (%)	21/113 (18.6)	64/583 (11.0)	85/696 (12.2)
Number of patients per unit			
N	113	581	694
Mean (SD)	14.6 (7.1)	11.4 (5.8)	11.9 (6.1)
Number of staff members per unit working dayshift			
N	113	582	695
Mean (SD)	4.2 (2.2)	3.6 (1.9)	3.7 (2.0)
Number of hours a physician is present per unit			
N	102	467	569
Mean (SD)	4.7 (4.5)	3.7 (4.7)	3.9 (4.6)

SD Standard deviation, *GMHR* General Medical Health Rating Scale, *PSMS* Physical Self-Maintenance Scale, *MMSE* Mini-Mental Status Evaluation, *CDR* Clinical Dementia Rating scale, *CSDD* Cornell Scale for Depression in Dementia, *NPI* Neuropsychiatric Inventory, *QUALID* Quality of Life in Late-Stage Dementia, *MOBID-II* Mobilization-Observation-Behaviour-Intensity-Dementia Pain Scale

[a] NPI-subsyndromes are calculated as the sum of the following items: NPI-Agitation = Agitation + Disinhibition + Irritability, NPI-Psychosis = Delusions + Hallucinations, NPI-Affective = Depression + Anxiety

95%CI:1,26–3.47, $p = 0.005$; OR = 1.05, 95%CI:1.00–1.10, $p = 0.045$ and OR = 1.09, 95%CI:1.04–1.14, $p < 0.001$, respectively). Older age was associated with lower odds of prescribing antidepressants (OR = 0.93, 95%CI:0.90–0.97, p < 0.001).

Younger age and higher NPI-psychosis subsyndrome score were significantly associated with higher odds of prescribing combined typical and atypical antipsychotics (OR = 0.96, 95%CI:0.92–0.99, $p = 0.023$ and OR = 1.11, 95%CI:1.05–1.17, $p < 0.001$, respectively).

Further, we found that with increasing values of NPI-affective subsyndrome score, the odds of prescribing anxiolytics were significantly higher (OR = 1.05, 95%CI: 1.01–1.10, $p = 0.026$).

Higher scores on the Charlson Comorbidity Index and NPI-apathy subsyndrome score were associated with lower odds of prescribing antidementia drugs (OR = 0.86, 95%CI:0.75–0.98, $p = 0.023$ and OR = 0.93, 95%CI: 0.86–1.00, $p = 0.039$, respectively). Compared to regular or respite and rehabilitation units, patients living in special care units had higher odds of being prescribed antidementia drugs (OR = 1.78, 95%CI:1.09–2.90, $p = 0.021$).

Discussion

Prevalence of PTD prescription was high overall for the majority of PTD categories, with the highest values for antidepressants; more than 60% of patients received at least one PTD throughout the study period. Our results are in line with previous findings showing how multi-psychotropic drug prescription is associated with severity of NPS [38], symptoms that are a common reason for institutionalization [39], and are persistent in NH patients [2].

In our study we found an increasing prevalence of antidepressants prescription, especially during the first six months after admission. Physicians might in fact promptly identify depression symptoms following NH admission, leading to an appropriate treatment and thereby lower mortality risk [40]. Antidepressants might also be frequently prescribed to treat a high level of NH patients whose depression is resistant to usual treatment with antidepressants, or with a wider indication to treat mood symptoms, such as anxiety and agitation, and not specifically depression [41].

Our study showed that among patients with dementia, up to 29.7% received sedatives/hypnotics and up to 20.8% received antipsychotics. Our findings stand in contrast to a similar study conducted in the USA, presenting a higher prevalence of antipsychotics prescription (28%) and a much lower prevalence of sedatives/hypnotics prescription (2%) [42]. Previous research has also shown a wide discrepancy in the prevalence of sedatives and hypnotics prescriptions in NHs [25, 28]. This

Table 2 Prevalence, incidence, and deprescribing rates of psychotropic drugs: numbers are percentages

Prevalence

	BL N = 113 (D-); 583 (D+); 696 (T)			6m N = 71 (D-); 437 (D+); 508 (T)			12m N = 53 (D-); 374 (D+); 427 (T)			18m N = 42 (D-); 307 (D+); 349 (T)			24m N = 34 (D-); 259 (D+); 293 (T)			30m N = 28 (D-); 209 (D+); 237 (T)			36m N = 24 (D-); 168 (D+); 192 (T)		
Drug category	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T
Antidepressants	28.3	28.5	28.4	33.8	38.9	38.2	35.8	40.6	40.0	40.5	40.1	40.1	38.2	42.5	42.0	39.3	42.6	42.2	45.8	41.7	42.2
Atypical antipsychotics	6.2	7.0	6.9	4.2	13.7	12.4	1.9	12.6	11.2	4.8	16.0	14.6	2.9	14.3	13.0	7.1	14.8	13.9	0	16.7	14.6
Typical antipsychotics	5.3	4.8	4.9	5.6	4.6	4.7	5.7	4.3	4.4	7.1	4.9	5.2	2.9	3.9	3.8	3.6	3.8	3.8	4.2	3.0	3.1
Any antipsychotic	10.6	11.7	11.5	8.5	18.1	16.7	7.5	16.8	15.7	11.9	20.8	19.8	5.9	17.8	16.4	10.7	18.2	17.3	4.2	19.6	17.7
Anxiolytics	16.8	15.4	15.7	23.9	20.6	21.1	28.3	21.1	22.0	33.3	23.5	24.6	29.4	21.2	22.2	21.4	19.1	19.4	29.2	19.6	20.8
Sedatives and hypnotics	35.4	22.5	24.6	47.9	29.7	32.3	49.1	23.5	26.7	50.0	23.1	26.4	47.1	23.6	26.3	50.0	18.7	22.4	45.8	22.6	25.5
Antidementia drugs	5.3	27.4	23.9	5.6	28.1	25.0	7.5	27.5	25.1	9.5	24.8	22.9	2.9	22.0	19.8	7.1	23.4	21.5	8.3	19.6	18.2
Cholinesterase inhibitors	2.7	20.2	17.4	4.2	19.5	17.3	5.7	18.4	16.9	7.1	16.3	15.1	2.9	13.1	11.9	3.6	13.9	12.7	4.2	11.9	10.9
At least one PTD[a]	59.3	63.0	62.4	66.2	71.6	70.9	77.4	72.2	72.8	76.2	72.6	73.1	73.5	71.8	72.0	75.0	69.4	70.0	75.0	68.5	69.3
Mean (SD)																					
Total medication - mean	7.3	5.7	6.0	8.2	6.2	6.5	7.5	6.0	6.2	7.2	5.9	6.1	7.3	6.2	6.3	7.2	6.3	6.4	7.8	6.3	6.5
(SD)	(3.5)	(3.1)	(3.2)	(3.5)	(3.0)	(3.1)	(3.4)	(3.0)	(3.1)	(3.6)	(3.3)	(3.3)	(3.5)	(3.3)	(3.3)	(3.9)	(3.3)	(3.4)	(3.9)	(3.7)	(3.7)
Total PTD[a] – mean	1.1	1.1	1.2	1.3	1.5	1.5	1.4	1.4	1.4	1.6	1.4	1.5	1.4	1.4	1.4	1.4	1.3	1.4	1.5	1.4	1.4
(SD)	(1.2)	(1.2)	(1.2)	(1.3)	(1.5)	(1.3)	(1.2)	(1.2)	(1.2)	(1.3)	(1.3)	(1.3)	(1.1)	(1.2)	(1.2)	(1.2)	(1.2)	(1.2)	(1.4)	(1.2)	(1.3)

Incidence[b]

	BL-6m N = 71 (D-); 437 (D+); 508 (T)			6m–12m N = 51 (D-); 346 (D+); 397 (T)			12m–18m N = 40 (D-); 298 (D+); 338 (T)			18m–24m N = 30 (D-); 246 (D+); 276 (T)			24m–30m N = 27 (D-); 200 (D+); 227 (T)			30m–36m N = 22 (D-); 156 (D+); 178 (T)		
Drug category	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T
Antidepressants	37.5	34.7	35.1	16.7	13.4	13.8	17.6	9.2	10.3	9.1	9.7	9.6	10.0	11.9	11.7	22.2	6.1	8.0
Atypical antipsychotics	33.3	60.0	58.7	0	28.9	28.3	0	23.4	22.9	100	16.7	18.9	100	20.0	25.0	0	7.1	7.1
Typical antipsychotic	25.0	50.0	45.8	0	37.5	31.6	33.3	40.0	38.9	0	11.1	10.0	0	0	0	0	0	0
Any antipsychotic	33.3	50.6	49.4	0	26.2	24.6	25.0	25.8	25.8	50.0	11.4	13.0	66.7	16.2	20.0	0	3.0	2.9
Anxiolytics	41.2	48.9	47.7	28.6	22.2	23.3	28.6	17.4	19.3	0	18.5	15.6	0	15.4	13.6	16.7	12.5	13.2
Sedatives and hypnotics	29.4	44.6	41.5	4.2	13.4	11.3	14.3	23.5	21.3	21.4	15.8	16.9	7.7	12.8	11.5	0	15.2	11.6
Antidementia drugs	50.0	26.8	27.6	0	8.3	8.0	0	8.1	7.8	0	8.9	8.8	0	6.5	6.4	0	9.4	8.8
Cholinesterase inhibitors	66.7	25.9	27.3	0	10.8	10.3	0	8.2	7.8	0	9.1	8.8	0	7.7	7.4	0	10.0	9.5

Deprescribing rates[b]

	BL-6m N = 71 (D-); 437 (D+); 508 (T)			6m–12m N = 51 (D-); 346 (D+); 397 (T)			12m–18m N = 40 (D-); 298 (D+); 338 (T)			18m–24m N = 30 (D-); 246 (D+) 276 (T)			24m–30m N = 27 (D-); 200 (D+); 227 (T)			30m–36m N = 22 (D-); 156 (D+); 178 (T)		
Drug category	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T
Antidepressants	8.5	7.1	7.3	6.1	5.4	5.5	4.3	8.9	8.4	5.3	7.0	6.8	11.8	8.6	9.0	7.7	7.8	7.8
Atypical antipsychotics	1.5	2.4	2.2	0	4.0	3.4	0	2.8	2.4	0	4.8	4.2	0	4.1	3.6	0	0.8	0.7
Typical antipsychotics	1.5	3.6	3.3	0	2.1	1.9	0	0.7	0.6	3.4	0.8	1.1	0	0	0	0	0.7	0.6

Table 2 Prevalence, incidence, and deprescribing rates of psychotropic drugs: numbers are percentages *(Continued)*

Any antipsychotic	3.1	5.0	4.7	0	5.3	4.5	0	3.4	2.9	3.6	5.4	5.2	0	4.3	3.7	0	0.8	0.7
Anxiolytics	1.9	7.2	6.5	10.8	3.3	4.2	0	6.1	5.5	5.0	6.8	6.6	13.6	7.5	8.2	0	3.2	2.9
Sedatives and hypnotics	13.5	7.5	8.1	14.8	8.0	8.6	21.1	8.3	9.2	18.8	4.8	5.9	14.3	7.5	8.0	16.7	4.1	5.2
Antidementia drugs	1.5	12.4	10.5	0	7.6	6.4	0	7.1	6.1	0	6.8	5.9	0	3.2	2.8	0	5.6	4.9
Cholinesterase inhibitors	1.5	8.2	7.1	0	6.4	5.5	0	5.2	4.5	0	3.8	3.3	0	2.3	2.0	0	4.4	3.8

D+: dementia at baseline; D-: no dementia at baseline; T: total
[a] PTD: psychotropic drugs
[b] Inclusion of cases with observations at both assessment points

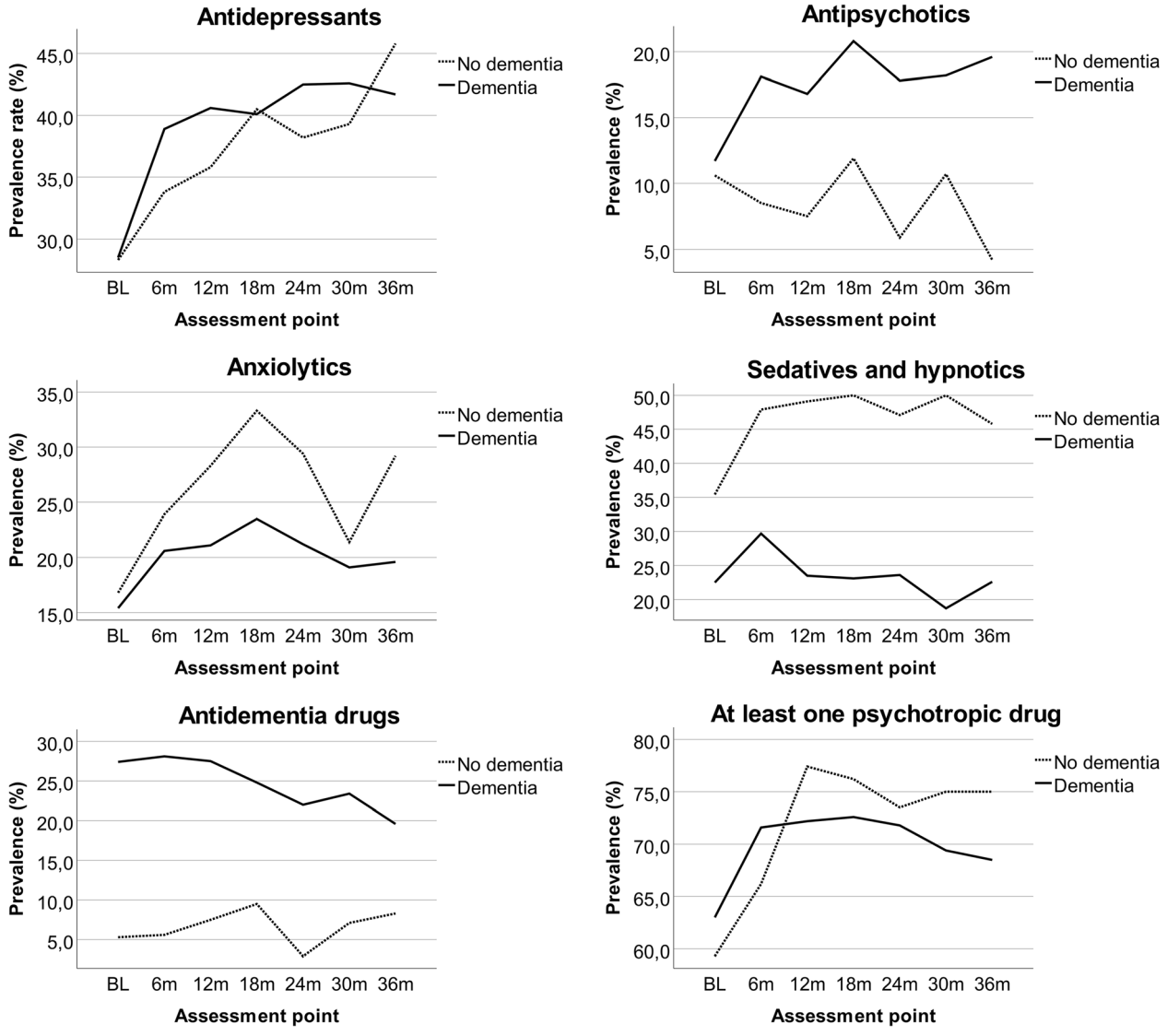

Fig. 2 Prevalence of psychotropic drugs prescription between baseline (BL) and 36 months (36m)

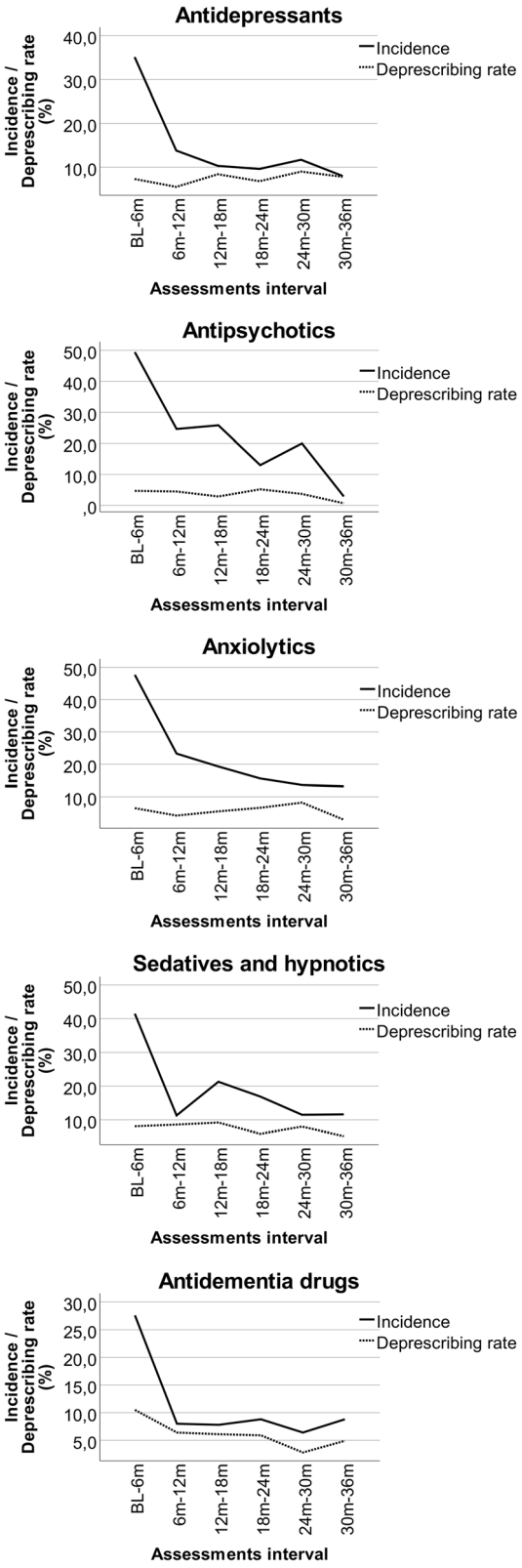

Fig. 3 Incidence and deprescribing rates of psychotropic drugs between baseline (BL) and 36 months (36m)

difference might have several explanations. A low prevalence of sedatives/hypnotics prescription might be compensated by a higher need to prescribe other medications with sedative effects, such as antipsychotics. On the other hand, sedation is a side effect of antipsychotics, making the use of sedatives/hypnotics less needed. Other factors such as nurses' distress related to NPS [8, 9], nurse/patient ratios [43], and differences in organizational culture can influence prescriptions of PTDs [44].

In our findings, the prevalence of antipsychotics prescription among people with dementia ranged between 11.7% and 20.7%, results that are higher than data from the UK (8.9%–9.2%) [45], lower than data from Switzerland (36.7%–47.3%) [27], but comparable with data from the USA (14.3%) [46]. A recent Canadian review summarized how both typical and atypical antipsychotics are associated with a higher mortality risk, although this risk is more unclear for atypical antipsychotics compared to typical ones [47]. Antipsychotics prescription has decreased in Norwegian NHs since 2004 [21], and our results confirm that the trend continues. This is probably due to the increases in warnings health authorities have given to limit the use of antipsychotics in people with dementia. It is reassuring that with increasing age, our study showed that the odds of prescribing antipsychotics decreased, as antipsychotics use is associated with a higher risk of adverse effects in older adults [48].

For every PTD category, we found the highest incidence rates between BL and 6m, with the highest values for antipsychotics. NPS are often a reason for NH admission [39], leading physicians to prioritize a pharmacological approach and quickly treat NPS. However, the high level of NPS during the first months might occur because patients need time to familiarize themselves with a new environment, and non-pharmacological approaches should be considered first. Deprescribing rates were relatively stable yet low during the follow-up period. Although caution should be applied while interpreting our results, stable deprescribing rates might still show that there is a focus on a regular medication review, trying to avoid unnecessary prescriptions over time.

Besides an expected significant association between depression, affective symptoms, and odds of being prescribed antidepressants, our study showed that patients with a higher level of affective symptoms had higher odds of being prescribed anxiolytics. This result is comparable with a recent cross-sectional study from the USA [42]. Anxiety is a common symptom of depression, which might be treated with anxiolytics as adjuvants, together with antidepressants.

We found a correlation between lower odds of being prescribed sedatives and hypnotics and increased severity of dementia measured with CDR sum of boxes.

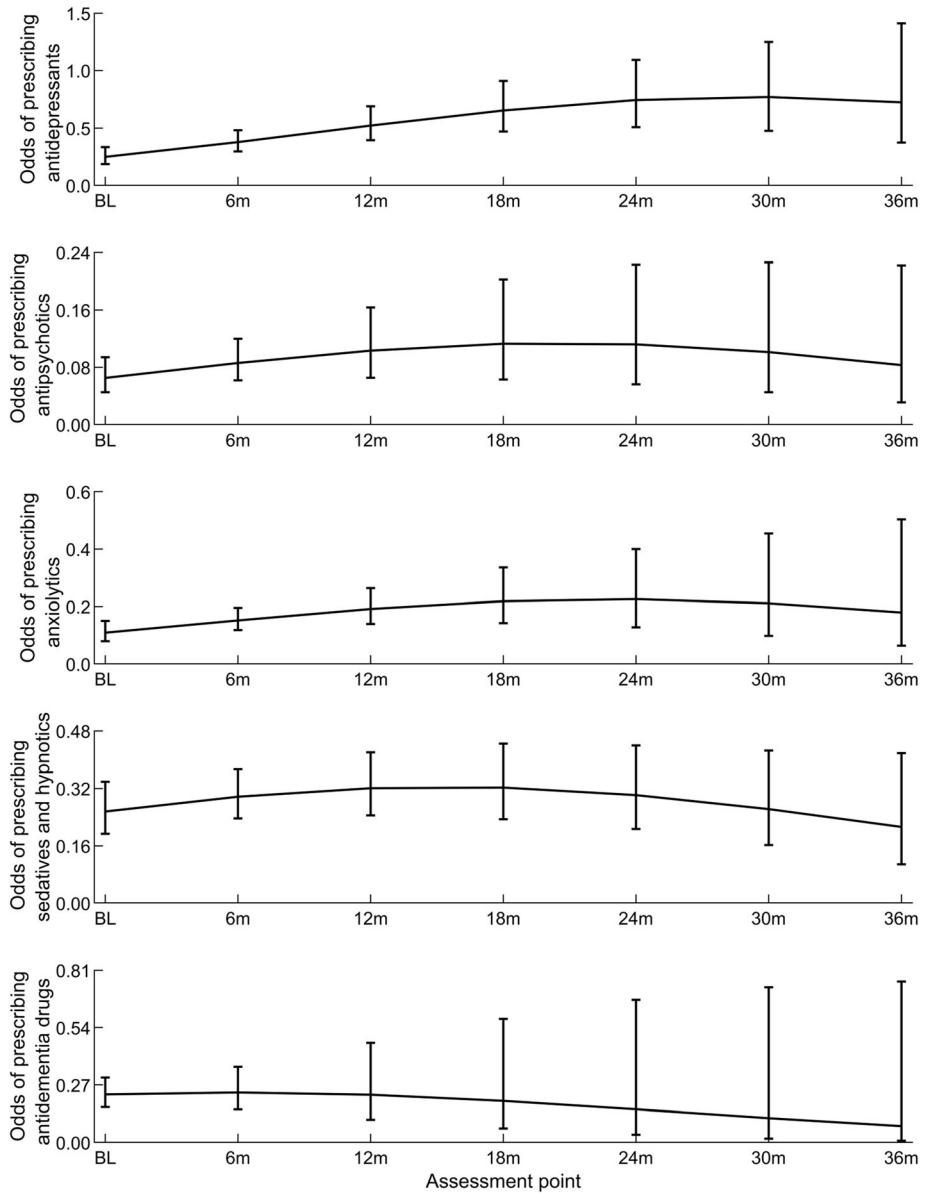

Fig. 4 Graphical representation of the unadjusted time trends for the odds of prescribing psychotropic drugs

Norwegian guidelines do not recommend people with dementia be prescribed sedatives or hypnotics [5], and our findings show a possible caution in prescribing sedatives and hypnotics for people with severe dementia. However, our results still show an alarmingly high prevalence of sedatives and hypnotics prescription during the duration of the study.

When modelling for the odds of prescribing sedatives and hypnotics, the only interaction found was between CSDD score and time. CSDD scores > 8 were associated with higher odds of prescribing sedatives and hypnotics from BL to 18m, and with lower odds of prescribing sedatives and hypnotics from 18m to 36m. A possible interpretation of these results might be that physicians show a more aggressive approach to treat depression with adjuvants, such as sedatives, during the first months after admission, while sedatives and hypnotics might not be considered to treat depression over time in older adults due to the risk of dependency and other side effects [15].

Antidementia drugs were less likely to be prescribed in patients with higher comorbidity. Antidementia drugs might possibly be avoided in patients with dementia who have high comorbidity and, subsequently, short life expectancy due to the risk of side effects. Another possible explanation might be that a large number of NH

Table 3 Results from the *generalized linear mixed model*[a] for antidepressants, antipsychotics, anxiolytics, sedatives/hypnotics, and antidementia drugs

Covariate	Antidepressants		Antipsychotics		Anxiolytics		Sedatives and hypnotics		Antidementia drugs	
	Reg. coeff. (SE)	***p*-value**	**Reg. coeff. (SE)**	***p*-value**	**Reg. coeff. (SE)**	***p*-value**	**Reg. coeff. (SE)**	***p*-value**	**Reg. coeff. (SE)**	***p*-value**
Time	**0.07 (0.02)**	**< 0.001**	0.04 (0.03)	0.157	**0.06 (0.02)**	**0.005**	−0.03 (0.03)	0.358	0.01 (0.02)	0.561
Time*Time	**−0.001 (0.0006)**	**0.023**	−0.001 (0.0008)	0.150	**−0.001 (0.0006)**	**0.029**	0.0009 (0.001)	0.374	−0.001 (0.0007)	0.135
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	**0.93 (0.90–0.97)**	**< 0.001**	**0.96 (0.92–0.99)**	**0.023**	0.98 (0.95–1.01)	0.172	1.02 (0.99–1.05)	0.213	0.97 (0.93–1.00)	0.062
Gender, female	**2.09 (1.26–3.47)**	**0.005**	1.17 (0.64–2.15)	0.608	0.99 (0.59–1.65)	0.961	0.90 (0.56–1.45)	0.676	1.01 (0.59–1.74)	0.973
Charlson Comorbidity Index	1.02 (0.91–1.14)	0.748	0.96 (0.60–1.53)	0.097	0.97 (0.87–1.09)	0.640	0.99 (0.89–1.09)	0.810	**0.86 (0.75–0.98)**	**0.023**
GMHR, Poor/Fair	1.04 (0.73–1.50)	0.824	0.96 (0.60–1.53)	0.851	1.17 (0.79–1.73)	0.440	0.74 (0.52–1.06)	0.104	0.78 (0.52–1.15)	0.207
PSMS	0.85 (0.72–1.01)	0.070	0.90 (0.72–1.13)	0.358	0.99 (0.82–1.19)	0.890	0.85 (0.72–1.01)	0.059	1.16 (0.96–1.39)	0.121
CDR sob	0.98 (0.93–1.04)	0.519	1.02 (0.95–1.09)	0.597	0.98 (0.93–1.04)	0.464	**0.89 (0.85–0.94)**	**< 0.001**	1.03 (0.97–1.09)	0.337
CSDD	**1.05 (1.00–1.10)**	**0.045**	0.98 (0.93–1.04)	0.590	1.02 (0.97–1.07)	0.411	**−0.06 (0.03)[b]**	**0.040**	0.95 (0.90–1.00)	0.075
CSDD * Time							**0.01 (0.004)[b]**	**0.010**		
CSDD * Time * Time							**−0.0003 (0.0001)[b]**	**0.014**		
NPI-agitation	1.00 (0.96–1.03)	0.868	1.00 (0.96–1.04)	0.980	1.01 (0.98–1.04)	0.626	0.99 (0.96–1.02)	0.446	0.97 (0.94–1.01)	0.136
NPI-psychosis	0.98 (0.93–1.03)	0.391	**1.11 (1.05–1.17)**	**< 0.001**	1.02 (0.97–1.07)	0.515	0.98 (0.93–1.04)	0.549	1.04 (0.98–1.09)	0.212
NPI-affective	**1.09 (1.04–1.14)**	**< 0.001**	1.03 (0.98–1.08)	0.227	**1.05 (1.01–1.10)**	**0.026**	1.04 (0.99–1.08)	0.083	1.00 (0.96–1.05)	0.929
NPI-caregivers	1.00 (0.95–1.04)	0.851	1.00 (0.95–1.05)	0.998	0.99 (0.94–1.03)	0.581	1.03 (0.98–1.08)	0.201	1.03 (0.98–1.09)	0.222
QUALID	0.97 (0.94–1.01)	0.094	1.01 (0.97–1.06)	0.541	1.02 (0.98–1.05)	0.416	1.03 (0.99–1.06)	0.134	1.00 (0.96–1.04)	0.827
NPI-apathy	1.04 (0.98–1.11)	0.175	1.00 (0.93–1.08)	0.984	0.98 (0.92–1.05)	0.657	1.03 (0.97–1.10)	0.265	**0.93 (0.86–1.00)**	**0.039**
Type of unit: special care unit	0.81 (0.50–1.30)	0.379	1.32 (0.75–2.34)	0.332	1.58 (0.98–2.57)	0.062	1.54 (0.96–2.45)	0.071	**1.78 (1.09–2.90)**	**0.021**
No. patients/unit	0.97 (0.93–1.00)	0.080	1.00 (0.95–1.05)	0.996	1.03 (0.99–1.07)	0.190	1.01 (0.98–1.05)	0.523	0.97 (0.93–1.01)	0.196
No. hours physician/unit	1.02 (0.97–1.07)	0.490	1.01 (0.95–1.07)	0.764	1.01 (0.97–1.06)	0.591	0.98 (0.93–1.03)	0.449	1.00 (0.95–1.06)	0.957

Bold text: statistically significant results. *GMHR* General Medical Health Rating Scale, *PSMS* Physical Self-Maintenance Scale, *CDR sob* Clinical Dementia Rating scale sum of boxes, *CSDD* Cornell Scale for Depression in Dementia, *NPI* Neuropsychiatric Inventory, *QUALID* Quality of Life in Late-Stage Dementia. NPI-subsyndromes are calculated as the sum the following items: NPI-Agitation = Agitation + Disinhibition + Irritability, NPI-Psychosis = Delusions + Hallucinations, NPI-Affective = Depression + Anxiety

[a] Multiple model; N = 1853(N = 476 at BL, N = 362 at 6m, N = 307 at 12m, N = 241 at 18m, N = 195 at 24m, N = 148 at 30m, N = 124 at 36m)

[b] Regression coefficient (SE) reported because of interaction

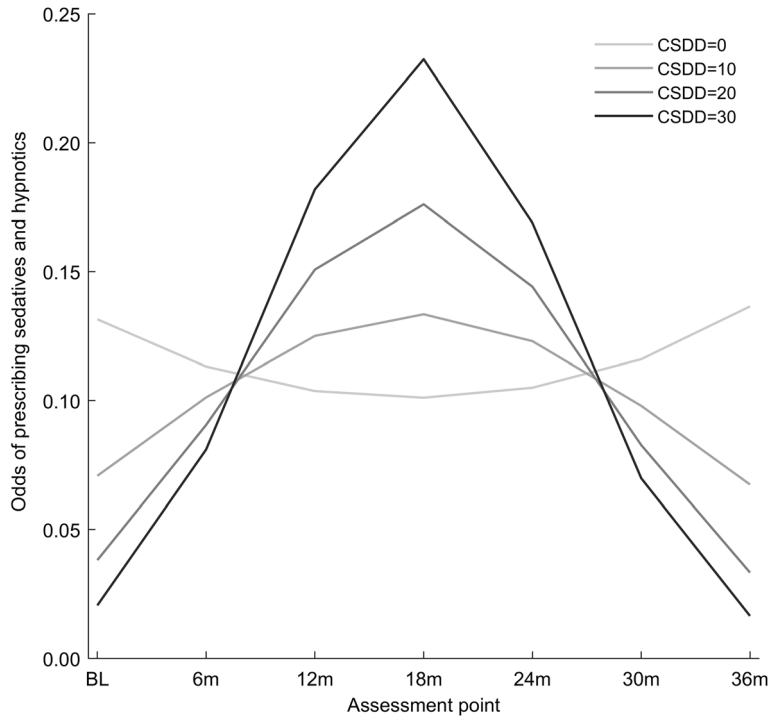

Fig. 5 Interaction between CSDD† score and change in odds of prescribing sedatives and hypnotics: graphical representation. Legends: † CSDD: Cornell Scale for Depression in Dementia

residents with psychiatric and somatic comorbidity have a potentially undetected dementia [49], leading physicians not to prescribe antidementia drugs to this group of patients. We found that patients with a higher degree of apathy were less likely to be prescribed antidementia drugs. Apathy might not be considered a symptom to be medicated, and a previous review showed that other behavioral symptoms, rather than apathy, were more sensitive to treatment with anti-dementia drugs [50]. However, a large meta-analysis has recently shown how cholinesterase inhibitors, although effective in treating cognitive symptoms in patients with Alzheimer's disease, did not improve NPS [51].

Due to the lack of longitudinal NH studies following prescription practices from admission, this study offers new information about PTD prescription over time, particularly its association with clinical and environmental factors. The short intervals between assessment points give a more accurate overview of prescription trends. The study used standardized and validated assessment tools, making it easy to compare results with other international studies.

This study has some limitations. Dementia status was primarily assessed according to BL data, but it was not assessed at the succeeding assessment points. Hence, we did not include dementia status as a covariate in the regression analysis. However, CDR was used as covariate and as indicator of cognitive impairment, and most participants in this study already had dementia at BL, making the dementia subgroup predominant. Inconsistencies might have been present during data collection, due to the high number of NH staff who assessed the participants, despite the use of standardized tools. However, the staff received extensive training prior to the study. About 50% of the eligible patients from the 47 included NHs did not participate in the study for different reasons, listed in detail in a previous paper [31]. Some participants dropped out or died during the follow-up period, resulting in a drastically reduced number of participants remaining at the later assessment points, and in this way affecting the power of the study. Due to reduced power, some potentially significant associations in multiple models might have been lost. By using a generalized linear mixed model to analyze the data, we minimized, to some extent, the bias due to missing data. However, a high drop-out rate might have introduced attrition bias, making difficult to distinguish the effects of covariates on the use of PTDs and attrition. We advise therefore a cautious interpretation of our data, as attrition bias may change the interpretation of the results from non-significant to significant [52]. The participants were recruited from different NHs. We did not present the distribution of the participants for each included NH. However, we considered the size of the ward in

which each participant was living, and included this information in the regression analysis. Data about medication "as needed" were unfortunately not recorded during data collection [31]. Even if many PTDs, i.e., antidepressants and antipsychotics, are commonly prescribed as regular medication, it is common in a clinical setting to prescribe sedatives / hypnotics and anxiolytics as needed. Thus, our study might present an underrepresentation for these drugs, and our results might underestimate the use of some PTD categories over time.

Conclusions

PTDs are extensively prescribed in NHs, already from admission, and there is an increasing trend of prescribing antidepressants and antipsychotics over time. Every PTD category had its highest incidence rate the first six months after NH admission. Higher age seems to decrease the risk of being prescribed antipsychotics, and severity of dementia seems to decrease the odds of being prescribed sedatives and hypnotics. Particular attention should be given to frequently assessing treatment with PTDs in NH patients to avoid prolonged and excessive exposure to these medications.

Abbreviations

PTD: Psychotropic drug; NH: Nursing home; NPS: Neuropsychiatric symptoms; BL: Baseline; 6m, 12m, 18m, 24m, 30m, 36m: 6-, 12-, 18-, 24-, 30-, 36-months follow-up, respectively; CI: Confidence interval; SE: Standard error; OR: Odds ratio

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Authors' contributions

EC and SB were responsible for the study concept and design. SB and GS collected the data. Analysis and interpretation of the data were conducted by JŠB, EC and SB. EC drafted the manuscript, while SB, GS, CG and JŠB were responsible for the critical revision of the manuscript for important intellectual content. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the sensitive nature of the data, but are available from the corresponding author on reasonable request and after approval by the Regional Committee for Medical and Health Research Ethics.

Declarations

Ethics approval and consent to participate

For participation, a signed informed consent was needed. NH personnel assessed the patients' capacity to consent to participate in the study. For patients with a clear capacity to consent, a signed informed consent was collected directly from the participants, but not from their next of kin. For patients with no capacity to consent, a signed informed consent from the participants' next of kin was collected. The Regional Committee for Medical and Health Research Ethics in South-Eastern Norway approved the study (2011/1738). The authors confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

GS has received honoraria for participating in a meeting of the Norwegian advisory board for Biogen, regarding the aducanumab trials. The other named authors have no competing interests, financial or otherwise.

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Publisher's Note

BMC Geriatrics
Oliver Cocks, Editor
BioMed Central, UK

March 11th 2022.

Dear Mr. Cocks,

I am writing to you regarding a recently published research article on BMC Geriatrics, titled: “Do prescription rates of psychotropic drugs change over three years from nursing home admission?”, *https://doi.org/10.1186/s12877-021-02437-x*

The authors have discovered an error in the analyses for the reported descriptive incidence and deprescribing rates for psychotropic drugs in Table 2, and consequently on the graphical representation in Figure 3. All the other analyses are double-checked and confirmed to be correct.

According to your journal policy, we wish to report this error, with the following correction note (“Errata”), as an attachment to this letter.

Incidence and deprescribing rates are reported as results and briefly discussed in the “Discussion” section, but were not the focus of our article. We believe that the corrected incidence and deprescribing rates do not change the interpretation of the results, nor the conclusions or the validity of the article. We apologize for this inconvenience, and we hope that the editorial board will consider to publish a correction note for the mentioned descriptive statistics.

Sincerely,

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Errata: corrections in text are marked in red.

Abstract, page 1, "Results" section, should read: Every PTD category had the highest incidence rate between admission and six months, and antidepressants had the highest values (18.9%). Deprescribing rates were generally highest between baseline and 6-months follow-up, except for sedatives and hypnotics.

Results, page 7-8, table 2, should read:

Table 2. Prevalence, incidence, and deprescribing rates of psychotropic drugs: numbers are percentages.

Prevalence

	BL N=113 (D-); 583 (D+); 696 (T)			6m N=71 (D-); 437 (D+); 508 (T)			12m N=53 (D-); 374 (D+); 427 (T)			18m N=42 (D-); 307 (D+); 349 (T)			24m N=34 (D-); 259 (D+); 293 (T)			30m N=28 (D-); 209 (D+); 237 (T)			36m N=24 (D-); 168 (D+); 192 (T)		
Drug category	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T
Antidepressants	28.3	28.5	28.4	33.8	38.9	38.2	35.8	40.6	40.0	40.5	40.1	40.1	38.2	42.5	42.0	39.3	42.6	42.2	45.8	41.7	42.2
Atypical antipsychotics	6.2	7.0	6.9	4.2	13.7	12.4	1.9	12.6	11.2	4.8	16.0	14.6	2.9	14.3	13.0	7.1	14.8	13.9	0	16.7	14.6
Typical antipsychotics	5.3	4.8	4.9	5.6	4.6	4.7	5.7	4.3	4.4	7.1	4.9	5.2	2.9	3.9	3.8	3.6	3.8	3.8	4.2	3.0	3.1
Any antipsychotic	10.6	11.7	11.5	8.5	18.1	16.7	7.5	16.8	15.7	11.9	20.8	19.8	5.9	17.8	16.4	10.7	18.2	17.3	4.2	19.6	17.7
Anxiolytics	16.8	15.4	15.7	23.9	20.6	21.1	28.3	21.1	22.0	33.3	23.5	24.6	29.4	21.2	22.2	21.4	19.1	19.4	29.2	19.6	20.8
Sedatives and hypnotics	35.4	22.5	24.6	47.9	29.7	32.3	49.1	23.5	26.7	50.0	23.1	26.4	47.1	23.6	26.3	50.0	18.7	22.4	45.8	22.6	25.5
Antidementia drugs	5.3	27.4	23.9	5.6	28.1	25.0	7.5	27.5	25.1	9.5	24.8	22.9	2.9	22.0	19.8	7.1	23.4	21.5	8.3	19.6	18.2
Cholinesterase inhibitors	2.7	20.2	17.4	4.2	19.5	17.3	5.7	18.4	16.9	7.1	16.3	15.2	2.9	13.1	11.9	3.6	13.9	12.7	4.2	11.9	10.9
At least one PTD[a]	59.3	63.0	62.4	66.2	71.6	70.9	77.4	72.2	72.8	76.2	72.6	73.1	73.5	71.8	72.0	75.0	69.4	70.0	75.0	68.5	69.3
Mean (SD)																					
Total medication - mean	7.3	5.7	6.0	8.2	6.2	6.5	7.5	6.0	6.2	7.2	5.9	6.1	7.3	6.2	6.3	7.2	6.3	6.4	7.8	6.3	6.5
(SD)	(3.5)	(3.1)	(3.2)	(3.5)	(3.0)	(3.1)	(3.4)	(3.0)	(3.1)	(3.6)	(3.3)	(3.3)	(3.5)	(3.3)	(3.3)	(3.9)	(3.3)	(3.4)	(3.9)	(3.7)	(3.7)
Total PTD[a] - mean	1.1	1.1	1.2	1.3	1.5	1.5	1.4	1.4	1.4	1.6	1.4	1.5	1.4	1.4	1.4	1.4	1.3	1.4	1.5	1.4	1.4
(SD)	(1.2)	(1.2)	(1.2)	(1.3)	(1.3)	(1.3)	(1.2)	(1.2)	(1.2)	(1.3)	(1.3)	(1.3)	(1.1)	(1.2)	(1.2)	(1.2)	(1.2)	(1.2)	(1.4)	(1.2)	(1.3)

Incidence[b]

	BL-6m N=71 (D-); 437 (D+); 508 (T)			6m-12m N=51 (D-); 346 (D+); 397 (T)			12m-18m N=40 (D-); 298 (D+); 338 (T)			18m-24m N=30 (D-); 246 (D+); 276 (T)			24m-30m N=27 (D-); 200 (D+); 227 (T)			30m-36m N=22 (D-); 156 (D+); 178 (T)		
Drug category	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T
Antidepressants	17.3	19.2	18.9	8.8	9.0	8.9	12.0	6.3	7.0	5.3	7.0	6.8	6.3	8.6	8.3	14.3	4.6	5.9
Atypical antipsychotics	1.5	8.9	7.8	0	4.3	3.7	0	4.3	3.7	3.3	2.9	3.0	7.4	3.6	4.1	0	1.6	1.3
Typical antipsychotic	1.5	2.4	2.3	0	1.8	1.6	2.6	2.1	2.2	0	0.4	0.4	0	0	0	0	0	0
Any antipsychotic	3.1	10.5	9.4	0	5.6	4.8	2.7	6.6	6.0	3.6	2.6	2.7	7.7	3.7	4.3	0	0.8	0.7
Anxiolytics	11.7	12.0	12.0	10.8	5.7	6.3	13.3	5.3	6.2	0	5.3	4.8	0	3.9	3.4	5.9	3.2	3.5
Sedatives and hypnotics	23.8	17.0	17.7	4.2	4.3	4.3	16.7	7.0	7.8	18.8	4.8	5.9	7.7	3.2	3.6	0	4.1	3.8
Antidementia drugs	2.9	10.7	9.3	0	3.3	2.8	0	2.8	2.4	0	2.7	2.4	0	2.0	1.7	0	2.5	2.1
Cholinesterase inhibitors	2.9	6.4	5.8	0	2.6	2.2	0	1.7	1.4	0	1.4	1.3	0	1.2	1.0	0	1.5	1.3

Deprescribing rates[b]

	BL-6m N=71 (D-); 437 (D+); 508 (T)			6m-12m N=51 (D-); 346 (D+); 397 (T)			12m-18m N=40 (D-); 298 (D+); 338 (T)			18m-24m N=30 (D-); 246 (D+) 276 (T)			24m-30m N=27 (D-); 200 (D+); 227 (T)			30m-36m N=22 (D-); 156 (D+); 178 (T)		
Drug category	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T	D-	D+	T
Antidepressants	21.1	14.6	15.4	11.8	8.2	8.6	6.7	12.9	12.2	9.1	9.7	9.6	18.2	11.9	12.6	12.5	10.1	10.4
Atypical antipsychotics	33.3	27.3	27.8	0	27.3	26.7	0	16.3	15.9	0	25.0	25.0	0	22.6	22.6	0	3.7	3.7
Typical antipsychotics	25.0	60.0	55.2	0	41.2	35.0	0	18.2	15.4	50.0	20.0	25.0	0	0	0	0	16.7	14.3
Any antipsychotic	33.3	31.6	31.7	0	25.0	23.4	0	14.8	14.0	50.0	22.0	23.1	0	18.4	17.9	0	3.0	2.9
Anxiolytics	9.1	35.2	31.7	28.6	13.8	16.5	0	19.7	17.3	9.1	22.8	20.6	37.5	26.7	28.3	0	12.5	10.8
Sedatives and hypnotics	17.2	24.2	22.6	14.8	22.8	21.0	18.2	26.8	24.7	21.4	15.8	16.9	14.3	26.1	23.3	16.7	15.2	15.6
Antidementia drugs	33.3	30.2	30.3	0	17.8	17.1	0	19.0	18.4	0	20.3	20.0	0	10.4	10.2	0	19.4	18.4
Cholinesterase inhibitors	50.0	31.5	31.9	0	23.7	22.8	0	22.4	21.7	0	21.1	20.5	0	14.3	13.8	0	25.0	24.0

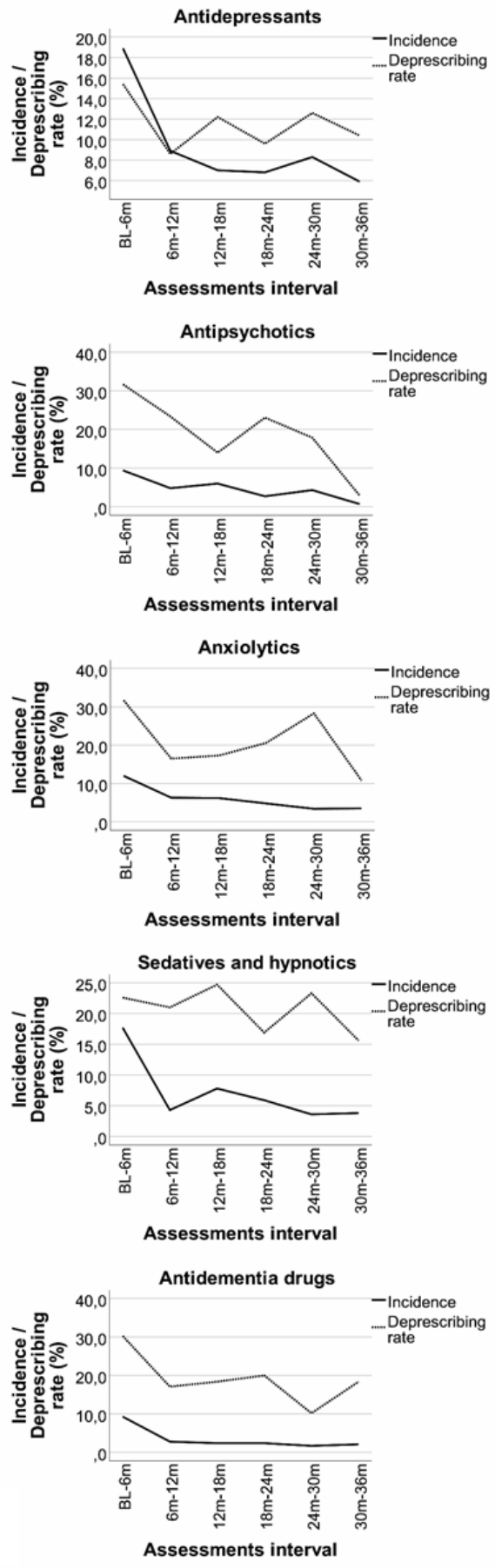
[a] PTD: psychotropic drugs

[b] Inclusion of cases with observations at both assessment points.

D+: dementia at baseline; D-: no dementia at baseline; T: total.

Results, page 9, Figure 3, should read:

Figure 3. Incidence and deprescribing rates of psychotropic drugs between baseline (BL) and 36 months (36m).



Legend: BL baseline; 6-, 12-, 18-, 24-, 30-, 36m: 6-, 12-, 18-, 24-, 30-, 36 months.

Discussion, page 9, should read: For every PTD category, we found the highest incidence rates between BL and 6m, with the highest values for antidepressants.

Deprescribing rates were highest between baseline and 6-months follow-up, except for sedatives and hypnotics with highest rates between 12-months and 18-months follow-up. Although caution should be applied while interpreting our results, generally higher deprescribing rates right after NH admission might still show that there is a focus on medication review, trying to avoid unnecessary prescriptions over time.

III

pharmacy

MDPI

Article

The Effect of the NorGeP–NH on Quality of Life and Drug Prescriptions in Norwegian Nursing Homes: A Randomized Controlled Trial

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Abstract: Background: The effect of the Norwegian General Practice–Nursing Home (NorGeP–NH) criteria has never been tested on clinical outcomes in nursing home (NH) residents. We performed a cluster-randomized trial in Norwegian NHs and tested the effect of NorGeP–NH on QoL (primary outcome), medication prescriptions, and physical and mental health (secondary outcomes) for the enrolled residents; Methods: Fourteen NHs were randomized into intervention NHs (iNHs) and control NHs (cNHs). After baseline data collection, physicians performed NorGeP–NH on the enrolled residents. We assessed the difference between cNHs and iNHs in the change in primary outcome from baseline to 12 weeks and secondary outcomes from baseline to eight and 12 weeks by linear mixed models; Results: One hundred and eight residents (13 lost to follow-up) and 109 residents (nine lost to follow-up) were randomized to iNHs and cNHs, respectively. Difference in change in QoL at 12 weeks between cNHs and iNHs was not statistically significant (mean (95% CI)): −1.51 (−3.30; 0.28), $p = 0.101$). We found no significant change in drug prescriptions over time. Difference in depression scores between cNHs and iNHs was statistically significant after 12 weeks. Conclusions: Our intervention did not affect QoL or drug prescriptions, but reduced depression scores in the iNHs. NorGeP–NH may be a useful tool, but its effect on clinical outcomes may be scarce in NH residents. Further studies about the effectiveness of NorGeP–NH in other healthcare contexts and settings are recommended.

Keywords: psychotropic polypharmacy; structured drug review; nursing homes

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1. Introduction

It is well established that polypharmacy, often defined as the use of more than five concomitant drugs [1], is prevalent in nursing homes (NHs) and is associated with frailty, hospitalization, cognitive and physical impairment, falls, and mortality [2,3].

In the past years, several explicit lists, such as Beers Criteria [4,5], START/STOPP [6], EU (7)-PIM [7], the PRISCUS list [8], and NorGeP [9], have been introduced to identify potentially inappropriate medications (PIM) in older adults. Medications may be inappropriate when their potential harm exceeds their benefit [10]. Over 30 PIM lists have been published between 1991 and 2017 aiming to identify the complexity of drug therapy in older people, but these lists have wide variability in what is considered a PIM [11]. This

variability can cause a big discrepancy in the detection of PIMs according to which list a clinician uses [12–14].

Several authors have approached this complexity by developing multifaceted interventions to avoid polypharmacy in older people, where medication review in an important aspect [15]. However, RCTs aiming to evaluate the effect of medication reviews on clinical, drug-related, and organizational outcomes are heterogeneous, do not always use standardized clinical outcomes, and lead to opposite or not always robust conclusions [16,17].

A recent meta-analysis of national and international studies showed that psychotropic polypharmacy, defined as the use of two-or-more or three-or-more psychotropic drugs (PTDs), is common in NH residents with dementia [18]. PTDs, such as antidepressants, antipsychotics, anxiolytics, sedatives, hypnotics, and antidementia drugs, may be used not only to treat primary psychiatric disorders, but also to mitigate neuropsychiatric symptoms (NPSs) associated with dementia. NPSs can be delusions, hallucinations, agitation, aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behaviors, and changes in appetite. According to national guidelines, clinicians should carefully assess the appropriateness of PTD prescribing in older people with dementia [19]. However, between 2000 and 2016, antipsychotics were the only PTD with reduced prescription in NH residents in Norway [20]. Despite a large variation in PTD prescriptions between different NHs, PTDs still cause about one-third of the detected drug-related problems among NH residents [21].

Although medication reviews can be helpful to reduce PTD prescriptions, it might not be clear if this reduction is clinically beneficial [22]. A recent cluster-randomized trial conducted in the Netherlands, for example, showed no reduction in PTD prescriptions and NPS occurrence despite a multidisciplinary intervention [23]. Similarly, another cluster-randomized trial conducted in German NHs, did not affect the prescription of potentially inappropriate medication or neuroleptic drugs, despite conducting a complex intervention [24]. Some studies have shown that when a medication review is performed by non-prescribers, such as pharmacists or external teams without the same knowledge of a resident as the primary physician, it might lead to a discrepancy between identified PIMs or suggested medication changes from pharmacists and the actual changes performed by a physician [22,25,26]. Therefore, it is important that healthcare personnel in NHs, including NH physicians, have sufficient knowledge about the correct use of PTDs in NH residents with psychiatric symptoms, and come to a joint decision, through team collaboration, about the necessary medication prescription after a medication review.

The Norwegian General Practice–Nursing Home (NorGeP–NH) is a list of criteria used to perform a medication review [27]. It is divided into three groups: single-substance criteria, drug–drug combination criteria, and criteria where regular consideration of "deprescribing" is of utmost importance in an NH population [27]. This list has previously been used to identify PIMs, but, as far as we are aware, it has never been tested in a "real-world" clinical setting, as a recent systematic review presented [28].

Self-perceived Quality of life (QoL) embraces many aspects of a person's physical and emotional health and gives a broader idea of the level of disease burden a person experiences. Measuring QoL in people with dementia can be challenging, as their level of insight might decrease as dementia worsens [29]. However, an observation-based scale such as QUALID has shown to be reliable and associated with depression, level of functioning, degree of dementia, agitation, and psychosis [30]. QoL, measured with either self-based or proxy-based tools, is associated with several clinical factors, including polypharmacy [31]. Despite a large number of assessment tools listing PIMs, only a few studies have presented the effect of PIM assessment tools on different persons' outcomes, and even fewer studies have explored a possible association between a specific PIM assessment tool and QoL [28]. In fact, only two PIM assessment tools have been explored and were found positively associated with an improvement in QoL [32,33].

The main objective of our study was to examine whether QoL (primary outcome) in NH residents could be influenced by exposing NH physicians to an educational program

about NorGeP–NH, after receiving a lecture on psychotropic drug use in older adults, and requesting them to perform a structured medication chart review with NorGeP–NH. As for secondary outcomes, we examined whether the same intervention influenced PTD and total medication prescriptions, cognitive function, NPS, physical health status, and functioning in daily living in the same group of residents.

2. Materials and Methods

2.1. Trial Design

We performed a cluster-randomized trial in 14 NHs, with a total of 42 wards, distributed in eight municipalities in Østfold county, Norway, between November 2018 and June 2019. NHs were treated as clusters, as the intervention was at staff/physician level and not at resident level. Primary and secondary outcomes were at resident level. The NHs were cluster-randomized into two groups, and the NHs were given the name of intervention NHs (iNHs) and control NHs (cNHs). Allocation was not revealed to the NH personnel until after completion of baseline data collection in order to minimize detection bias at baseline. Many of the chosen assessment tools needed to be administered by nurses/authorized social workers who knew the participants well and who had observed the participants over time. Thus, it was not possible to blind data collectors after the intervention was delivered. The report of this trial follows the recommendations of CONSORT (Consolidated Standards of Reporting Trials) guidelines and CONSORT extension to cluster-randomized trials [34]. The described intervention follows the TIDieR criteria [35].

Every participant gave written informed consent to be included in the trial. The capacity to consent was evaluated by a clinical examination performed first by the NH physician, and confirmed by the first author, to detect the participant's ability to understand and weigh the given information, reason, and give an explicit choice. In case of doubt, clinicians could use the Aid to Capacity Evaluation (ACE) form [36]. If participants had reduced capacity to consent, a written informed consent was obtained from the participant's next of kin. The Regional Committee for Medical and Health Research Ethics (2017/2171 REK south-east D) approved the trial. The study was registered on 6 November 2018, on clinicaltrials.gov (accessed on 9 January 2022) (NCT03736577).

2.2. Participants

Before inclusion, all 19 municipalities in the district served by the regional Østfold Hospital, with a total of 34 long-term care NHs, received information about the study protocol and were invited to participate. Those responsible for healthcare services in every municipality decided which nursing home(s) could participate. Once the participating NHs were determined, the responsible NH physicians were informed about eligibility criteria to include the NH residents in this study. Eligibility criteria were (a) NH resident and (b) expected to live in the NH for more than 12 weeks. Exclusion criteria were (a) terminal disease, (b) severe somatic or psychiatric disease where the resident was too debilitated or not able to cooperate or where the examination would cause too great of a psychological and physical burden (i.e., severe psychotic state), and (c) the physician had performed a structured drug review for the participant within three months prior to inclusion. NH physicians were thoroughly informed about these criteria and were responsible for assessing eligibility.

Prior to baseline data collection and randomization, the healthcare personnel from both iNHs and cNHs participated in a three-hour lecture on dementia and dementia-related neuropsychiatric symptoms, delirium, depression, anxiety, and psychosis in older people. In addition, we asked each participating nursing home to dedicate one or two NH personnel per ward to collect data. The data collectors were nurses or authorized social workers, and they participated in a three-hour lecture to learn how to use validated assessment tools. The assessment tools were either interview-based or proxy-based, and they are described later. The first author gave both lectures. Clinical data about

the residents in both iNHs and cNHs were collected eight and 12 weeks after baseline data collection.

2.3. Intervention

The intervention was an *educational intervention* on nursing home physicians, followed by a *drug chart review* of the participant's medications, and included the following steps:

(1) Physicians in the iNHs attended a three-hour lecture including the following subjects:

- principles of pharmacology in older people;
- the use of PTDs in older people;
- how to conduct a drug chart review with the Norwegian General Practice–NH (NorGeP–NH) criteria [27].

This lecture was held by a psychiatrist (first author) after baseline data were collected. The lecture was held in the nursing home where the physicians worked. It was held face-to-face and included an electronic presentation as supportive material. The physicians who attended the lecture were given a copy of the electronic presentation after the lecture, and they received a laminated NorGeP–NH list to use in the following step.

(2) Within a two-week period after the lecture, physicians in the iNHs performed a drug chart review according to NorGeP–NH. Physicians were allowed to consult a psychiatrist (first author) in case they needed to discuss choices made during a review, but the final decision about medication changes was the physician's responsibility.

2.4. Control Group

The physicians and healthcare personnel in the cNHs were asked to follow-up residents as usual. If medication changes were necessary, physicians could do so, but without using a structured drug review chart during the follow-up period. After the last assessment at 12 weeks, as a courtesy to the physicians in the cNHs they were given the same lecture as described in (1).

2.5. Collected Data and Outcomes

The primary outcome was the difference between cNHs and iNHs in change in quality of life (QoL) assessed with the Quality of Life in Late-Stage Dementia (QUALID) scale [30,37], from baseline to 12-week follow-up. The secondary outcomes were the difference between cNHs and iNHs in change from baseline to 8–12 weeks in the number of drugs prescribed daily, the number of prescribed pro re nata (PRN) drugs, the prescription of psychotropic drugs categories (antidepressants, antipsychotics, anxiolytics, sedatives/hypnotics, and antidementia drugs), and in clinical scores measuring the level of depression, cognitive function, neuropsychiatric symptoms, physical health status, and functioning in daily living. Table 1 reports the instruments used to collect the data. We also collected demographic data and nursing home characteristics for each participating resident (Table 2 in Results section).

Table 1. Structured interviews and checklists used to collect data [a].

Clinical Feature	Assessment Tools	Method of Collection	Ranging Score	Comments
Cognitive function	Montreal Cognitive Assessment (MoCA)	Interview	0–30	A higher score indicates better cognitive function [38].
	Clinical Dementia Rating (CDR) scale	Proxy-based	0–3	Total score is calculated using a complex algorithm. CDR = 0: no dementia; CDR = 0.5, 1, 2, or 3 indicates questionable, mild, moderate, or severe cognitive impairment [39].

Table 1. *Cont.*

Clinical Feature	Assessment Tools	Method of Collection	Ranging Score	Comments
Neuropsychiatric symptoms	Neuropsychiatric Inventory 12-item Nursing Home Version (NPI-NH) [b]	Proxy-based	0–144	Single-item score is calculated by multiplying severity (score 1–3) by frequency (score 1–4). Total score is the sum of all the single-item scores [40–42]. We calculated the NPI-NH subsyndrome scores for agitation, psychosis and affective symptoms [b].
	Cornell Scale for Depression in Dementia (CSDD)	Proxy-based	0–38	Total score is calculated by summing up 19 single-item scores. Each single item can be scored 0, 1 or 2 (symptom not present, moderate or periodically present, severe). A higher score indicates more severe symptoms [43].
	Montgomery and Asberg Depression Rating Scale (MADRS)	Interview	0–60	Total score is calculated by summing up 10 single-items scores (0–6). A higher score indicates more severe symptoms [44].
	Geriatric Anxiety Inventory (GAI)	Interview	0–20	A 20-item self-report or nurse-administered scale. A higher score indicates more anxiety-related symptoms [45].
Medication	Anatomic Therapeutic Chemical (ATC) classification system	Medication chart in resident's journal	N/A	We calculated the total amount of daily prescribed drugs, and the total amount of prescribed pro re nata (PRN) drugs. We collected data on prescribed psychotropic drugs, and we grouped them as antipsychotics (N05A except lithium), antidepressants (N06A), anxiolytics (N05B), hypnotic/sedatives (N05C), and anti-dementia medication (N06D).
Physical health status	General Medical Health Rating (GMHR) scale	Proxy-based	Excellent, good, fair, poor	Used to assess the general medical health status of each participant, according to the amount of stable/unstable medical conditions, the number of prescribed drugs and the general clinical condition [46].
	Charlson Comorbidity Index	N/A	0–30	A scale divided into 18 items/groups of diseases. Each item is scored yes/no, assuming the value of 1/0. An algorithm calculates the total score. Higher values indicate a higher level of comorbidity [47].
	Timed "Up and Go" test (TUG)	N/A	N/A	It measures the ability to stand up from a sitting position, walk a predefined distance, and sit down again. The score is in seconds and calculated as the average of two performances [48].

Table 1. *Cont.*

Clinical Feature	Assessment Tools	Method of Collection	Ranging Score	Comments
Functioning in daily living and quality of life (QoL)	Physical Self-Maintenance Scale (PSMS)	Proxy-based	1–6	A 6-item scale to measure the level of functioning. Each item is scored 1 only if there is no decline. A higher score indicates a higher level of functioning [49].
	Quality of Life in Late-Stage Dementia scale (QUALID)	Proxy-based	11–55	A 11-item assessment scale, where lower scores indicate a higher QoL [30,37].

[a] Data were collected by nurses/authorized social workers. [b] A previous principal component analysis identified the NPI-NH subsyndromes: NPI-NH agitation (agitation/aggression, disinhibition, and irritability), NPI-NH psychosis (delusions and hallucinations), and NPI-NH affective (depression and anxiety) [50].

2.6. Sample Size

In a previous Norwegian study, people admitted to an NH had a QUALID score of 20.0 (SD 7.2) [51]. When the study was designed, to the best of our knowledge, there were no previous randomized controlled studies using QUALID score as a primary outcome. Thus, to be sure that any possible change caused by our intervention was clinically relevant, we chose to define a change from baseline to 12-week follow-up in QUALID score of 33% as of clinical importance prior to power calculations. With an 80% power and 0.05 significance level, and assuming SD 7.2 in both groups at baseline and follow-up, 39 residents needed to be included in each allocation group to detect a 33% difference between iNHs and cNHs in change from baseline to 12-week follow-up in QUALID score. In Norwegian NHs, about one out of four residents die every year [52]. Thus, we estimated a 6–7% drop-out rate due to death within a 12-week period. Rounding up the drop-out rate to 10%, 43 residents had to be included in each allocation group. Assuming 10 participating NHs and a cluster effect on NH level of about 5%, the final number of residents was estimated to be 60 in each group. Because of uncertainty about how many NHs would decide to participate in the study, we aimed to include about 100 residents in each allocation group.

2.7. Randomization

An independent statistician allocated the participating NHs into two arms by performing a stratified randomization using a computer-generated algorithm. To avoid contamination bias, every NH was treated as a cluster. Each NH was under the care of one physician or group of physicians who worked together and only in that NH. All the participating NHs were stratified into four groups. Stratification was performed according to the number of participants the personnel in each NH were able to include and follow up. The allocation results were kept in a digital safe, hidden from NH physicians responsible for enrolling participants. NH physicians were asked to assess each resident in the participating NH for eligibility, and they were responsible for enrolling participants. One of the authors (EC) verified the eligibility criteria by discussing them with the NH physician/NH personnel and verified the participants' capacity to consent. If an NH had limited resources to follow up participants, NH leaders and physicians were asked, before inclusion and allocation, to determine how many residents they could possibly enroll and follow up. In this case, the predetermined number of residents was selected by drawing lots. This process was performed by EC in the presence of at least one healthcare personnel from the selected NH.

Once NHs were allocated and residents were enrolled, a random-number generator was used to determine which allocation group was given the intervention. The result of this process was also kept hidden from NH physicians and healthcare personnel until after baseline data were collected. Once baseline data were collected, the first author informed the physicians who were working in the intervention NHs and carried out the intervention together with them.

2.8. Statistical Methods

The statistical analyses were performed by using SPSS© v27 and SAS© v9.4. Baseline characteristics are presented as means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables. We present the total amount of prescribed drugs as means (SDs) both for daily prescriptions and for pro re nata (PRN) drugs. PTD prescriptions are presented as frequencies and percentages at each assessment point. For the primary and secondary analyses, we included participants who had data available at baseline. To assess the difference between iNHs and cNHs in the change in primary and secondary continuous outcomes, we estimated linear mixed models with fixed effects for time, allocation group, and interaction between these two. To assess the difference in change for categorical outcomes, we estimated generalized linear mixed models with the same fixed effects. All models contained random effects for NHs to adjust the estimates for cluster effect at the NH level, which was non-negligible according to the intra-class correlation coefficient. For continuous outcomes, the results were presented as mean change within allocation groups and mean difference in change between the groups with corresponding 95% confidence interval (CI) and *p*-value. For categorical outcomes, the results were presented as odds for change within the allocation group as well as odds for differences in change between groups with 95% CI and *p*-values. We set the level of significance at 5%.

3. Results

Figure 1 shows the flow diagram of the trial. Two hundred and seventeen residents were included at baseline between November 2018 and March 2019. Six hundred and three residents from 15 NHs in the nine municipalities that agreed to participate in the trial were recruited and assessed for eligibility. Among these, 437 met inclusion criteria. One NH in one municipality, which had originally agreed to participate with 14 residents, withdrew from the trial during eligibility assessment due to a lack of local NH resources. Fifty residents declined to participate, 161 residents were excluded by drawing lots because some NHs could not include more than a predetermined number of residents (see Section 2.7), six residents died right before baseline assessment, and one resident moved from the NH right before baseline assessment. Two residents were excluded for violation of protocol, as the NH never returned the assessment documentation. Sixteen NH physicians were involved in the trial, seven working in the cNHs and nine working in the iNHs.

Table 2 reports demographics, NH characteristics, and clinical scores at baseline. Residents were on average (SD) 84.6 (9.4) and 83.3 (8.0) years old in the cNHs and iNHs, respectively. Most residents in the control group lived in regular units (56.9%), while most residents in the intervention group lived in special care units (59.3%). The two groups had a comparable number of residents per unit (15.07 in cNHs vs. 13.15 in iNHs), number of staff members per unit during the day shift (4.73 in cNHs vs. 4.61 in iNHs), and physicians worked on average 0.88 more hours in cNHs compared to iNHs (6.43 h in cNHs vs. 5.55 h in iNHs). According to CDR, most participants had either mild cognitive impairment (7.8% in cNHs and 7.7% in iNHs) or dementia (89.3% in cNHs and 92.3% in iNHs). The average (SD) number of prescribed daily drugs was 6.92 (3.49) for participants living in the cNHs and 7.55 (3.04) for participants living in the iNHs. The average number (SD) of prescribed pro re nata (PRN) drugs was 4.04 (2.74) for the cNHs and 4.72 (2.89) for the iNHs. For some of the assessment scores, such as MoCA, CSDD, QUALID or TUG, there was a considerable amount of missing data. This aspect is discussed later.

Results from the primary analysis, assessing the difference in change in QoL, are presented in Table 3. We found no statistically significant difference between cNHs and iNHs in change in QoL from baseline to 12-week follow-up. However, while the QUALID score remained stable in the iNHs, we found a statistically significant increase in QUALID score (higher QUALID score indicates lower QoL) in the cNHs ($p = 0.013$).

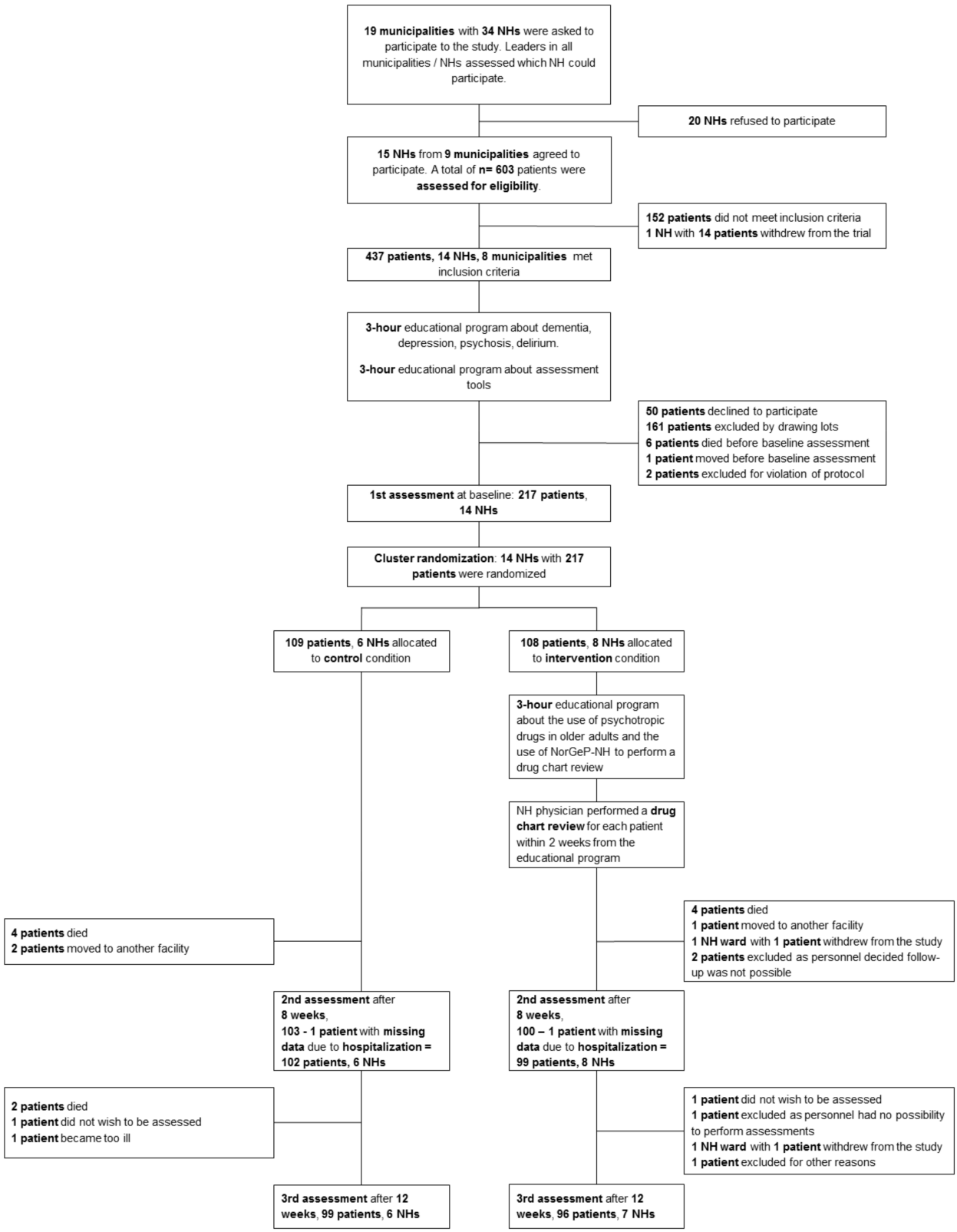

Figure 1. Flowchart of the trial. NH, nursing home.

Table 2. Demographics, nursing home characteristics, and clinical scores at baseline.

	Control NHs (*n* = 109) [a]	Intervention NHs (*n* = 108) [a]
Age		
Mean (SD)	84.57 (9.43)	83.33 (7.97)
Gender		
Female, *n* (%)	78 (71.6)	61 (56.5)
Type of unit, *n* (%)		
Regular [b]	62 (56.9)	44 (40.7)
Special care [c]	33 (30.3)	64 (59.3)
Other	14 (12.8)	0 (0)
Number of residents per unit		
Mean (SD)	15.07 (4.41)	13.15 (3.97)
Number of staff members per unit on day shift		
Mean (SD)	4.73 (1.80)	4.61 (1.79)
Physician hours per week		
Mean (SD)	6.43 (1.68)	5.55 (3.52)
CDR, *n* (%)	*n* = 103	*n* = 104
0–no dementia	3 (2.9)	0 (0)
0.5–questionable cognitive impairment	8 (7.8)	8 (7.7)
1.0–mild cognitive impairment	30 (29.1)	20 (19.2)
2.0–moderate cognitive impairment	28 (27.2)	32 (30.8)
3.0–severe cognitive impairment	34 (33)	44 (42.3)
Charlson Comorbidity Index	*n* = 108	*n* = 101
Mean (SD)	2,54 (1.96)	2.57 (1.68)
CSDD	*n* = 94	*n* = 87
Mean (SD)	6.50 (5.84)	7.46 (5.99)
MADRS	*n* = 78	*n* = 45
Mean (SD)	9.03 (7.80)	7.47 (6.67)
GAI	*n* = 81	*n* = 56
Mean (SD)	5.58 (5.70)	5.0 (5.32)
GMHR, *n* (%)	*n* = 106	*n* = 99
Poor	0 (0)	11 (11.1)
Fair	44 (41.5)	50 (50.5)
Good	37 (34.9)	19 (19.2)
Excellent	25 (23.6)	19 (19.2)
MoCA	*n* = 79	*n* = 73
Mean (SD)	10.66 (6.97)	7.08 (6.44)
NPI-Total score	*n* = 107	*n* = 104
Mean (SD)	17.10 (19.10)	21.92 (21.30)
NPI-Caregiver	*n* = 107	*n* = 104
Mean (SD)	6.92 (8.50)	9.48 (10.49)
NPI-Affective [d]	*n* = 107	*n* = 101
Mean (SD)	3.58 (5.46)	4.15 (5.42)
NPI-Psychosis [d]	*n* = 101	*n* = 102
Mean (SD)	1.93 (3.72)	3.51 (4.73)
NPI-Agitation [d]	*n* = 107	*n* = 104
Mean (SD)	5.26 (8.38)	8.20 (9.48)
PSMS		
Mean (SD)	1.06 (1.31)	1.16 (1.29)
QUALID	*n* = 97	*n* = 106
Mean (SD)	21.31 (6.72)	23.27 (8.03)
TUG	*n* = 40	*n* = 36
Mean (SD)	26.81 (16.67)	27.52 (20.36)
Number of daily medications		
Mean (SD)	6.92 (3.49)	7.55 (3.04)
Number of PRN drugs	*n* = 106	*n* = 107
Mean (SD)	4.04 (2.74)	4.72 (2.89)

[a] A lower *n* is specified in case of missing cases. [b] General NH wards often dedicated to people with somatic diseases who need continuous assistance. [c] NH ward with a higher resident:staff ratio, often dedicated to people with a severe degree of dementia and neuropsychiatric symptoms. [d] NPI-subsyndromes are calculated as the sum of the following items: NPI-Agitation = Agitation + Disinhibition + Irritability; NPI-Psychosis = Delusions + Hallucinations; NPI-Affective = Depression + Anxiety. CDR, Clinical Dementia Rating scale; CSDD, Cornell Scale for Depression in Dementia; GAI, Geriatric Anxiety Inventory; GMHR, General Medical Health Rating Scale; MADRS, Montgomery and Asberg Depression Rating Scale; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; PRN, pro re nata; PSMS, Physical Self-Maintenance Scale; QUALID, Quality of Life in Late-Stage Dementia; SD, standard deviation; TUG, Timed "Up and Go" test.

Table 3. Analyses of primary outcome [a]: Difference in change in QoL assessed with QUALID, baseline to 12 weeks.

	Control NHs	Intervention NHs
Baseline		
n	97	106
Mean (SD)	21.31 (6.72)	23.27 (8.03)
Week 12		
n	84	95
Mean (SD)	22.74 (7.64)	23.11 (8.72)
Mean change (95% CI)	−1.69 (−3.00; −0.38)	−0.18 (−1.43; 1.07)
Mean difference in change (95% CI)	−1.51 (−3.30; 0.28)	
p-value	0.101	

[a] Mean change in QUALID score within groups and mean difference in change between iNHs and cNHs derived from results of a linear mixed model: QoL, quality of life; QUALID, Quality of Life in Late-Stage Dementia; CI, confidence interval; SD, standard deviation.

Results from the analyses of secondary outcomes (see paragraph "Outcomes" and Table 1 for details) are presented in Table 4 for clinical measures and Table 5 for prescribed drugs. Compared to the control group, residents in the iNHs had a significantly larger reduction in CSDD score from BL to week 12 (mean difference in change (95% CI) −2.59 (−3.95; −1.23), $p < 0.001$). We found no statistically significant difference between the two groups in change in the prescription of PTD categories (antidepressants, antipsychotics, anxiolytics, sedatives/hypnotics, and antidementia drugs treated as groups).

Table 4. Analyses of secondary outcomes [a]: difference in change in clinical outcomes from baseline to Week 8/Week 12.

	Control NHs		Intervention NHs	
QUALID	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	97	21.31 (6.72)	106	23.27 (8.03)
Week 8	89	22.45 (7.96)	97	24.03 (8.83)
Week 12	84	22.74 (7.65)	95	23.11 (8.72)
Mean change (95% CI)				
Baseline to Week 8	−1.26 (−2.36; −0.16)		−1.14 (−2.21; −0.07)	
Baseline to Week 12	−1.75 (−2.89; −0.61)		−0.21 (−1.30; 0.88)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.12 (−1.62; 1.38)		0.876	
Baseline to Week 12	−1.54 (−3.08; 0.01)		0.052	
CSDD	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	94	6.50 (5.84)	87	7.46 (5.99)
Week 8	86	7.38 (6.19)	72	7.60 (6.91)
Week 12	77	6.49 (5.75)	60	5.80 (5.39)
Mean change (95% CI)				
Baseline to Week 8	−1.09 (−1.96; −0.22)		−0.05 (−1.02; 0.91)	
Baseline to Week 12	−0.73 (−1.66; 0.20)		1.86 (0.82; 2.90)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−1.03 (−2.29; 0.23)		0.109	
Baseline to Week 12	−2.59 (−3.95; −1.23)		<0.001	
MADRS	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	78	9.03 (7.80)	45	7.47 (6.67)
Week 8	66	10.59 (8.17)	22	7.27 (5.18)
Week 12	65	10.05 (7.83)	16	7.88 (6.62)
Mean change (95% CI)				
Baseline to Week	−1.81 (−3.06; −0.56)		0.17 (−1.90; 2.23)	
Baseline to Week 12	−0.98 (−2.34; 0.38)		−0.10 (−2.62; 2.41)	

Table 4. *Cont.*

	Control NHs		Intervention NHs	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−1.98 (−4.36; 0.40)		0.106	
Baseline to Week 12	−0.88 (−3.69; 1.94)		0.542	
NPI-Agitation subsyndrome [b]	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	107	5.26 (8.38)	104	8.20 (9.48)
Week 8	98	6.70 (9.52)	92	8.64 (9.68)
Week 12	92	6.27 (9.06)	85	8.73 (10.21)
Mean change (95% CI)				
Baseline to Week 8	−1.22 (−2.57; 0.14)		−0.41 (−1.83; 1.01)	
Baseline to Week 12	−1.12 (−2.53; 0.29)		−0.46 (−1.93; 1.02)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.81 (−2.72; 1.11)		0.409	
Baseline to Week 12	−0.66 (−2.65; 1.32)		0.514	
NPI-Psychosis subsyndrome [b]	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	101	1.93 (3.72)	102	3.51 (4.73)
Week 8	92	1.95 (3.45)	90	4.07 (5.88)
Week 12	85	1.85 (3.75)	81	4.30 (6.17)
Mean change (95% CI)				
Baseline to Week 8	−0.20 (−0.92; 0.51)		−0.55 (−1.28; 0.19)	
Baseline to Week 12	−0.25 (−0.99; 0.50)		−0.57 (−1.34; 0.20)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	0.35 (−0.65; 1.35)		0.497	
Baseline to Week 12	0.32 (−0.73; 1.37)		0.548	
NPI-Affective subsyndrome [b]	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	107	3.58 (5.46)	101	4.15 (5.42)
Week 8	96	4.94 (6.78)	90	4.76 (6.48)
Week 12	90	4.41 (6.12)	84	5.04 (7.04)
Mean change (95% CI)				
Baseline to Week 8	−1.19 (−2.16; −0.23)		−0.67 (−1.67; 0.32)	
Baseline to Week 12	−0.95 (−1.93; 0.04)		−0.86 (−1.88; 0.16)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.52 (−1.90; 0.86)		0.459	
Baseline to Week 12	−0.09 (−1.50; 1.33)		0.907	
NPI-Total score	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	107	17.10 (19.10)	104	21.92 (21.30)
Week 8	98	20.11 (21.73)	92	23.79 (25.45)
Week 12	99	16.61 (19.25)	91	23.33 (27.45)
Mean change (95% CI)				
Baseline to Week 8	−2.85 (−5.90; 0.20)		−2.22 (−5.39; 0.96)	
Baseline to Week 12	0.48 (−2.59; 3.54)		−1.75 (−4.95; 1.45)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.63 (−4.98; 3.71)		0.775	
Baseline to Week 12	2.22 (−2.15; 6.59)		0.319	
NPI-Caregiver	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	107	6.92 (8.50)	104	9.48 (10.49)
Week 8	98	7.73 (8.31)	92	9.57 (11.26)
Week 12	92	7.11 (8.49)	85	9.88 (12.05)
Mean change (95% CI)				
Baseline to Week 8	−0.79 (−1.97; 0.38)		−0.16 (−1.41; 1.08)	
Baseline to Week 12	−0.48 (−1.71; 0.76)		−0.19 (−1.49; 1.11)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.63 (−2.28; 1.02)		0.454	

Table 4. *Cont.*

	Control NHs		Intervention NHs	
Baseline to Week 12	−0.29 (−2.01; 1.43)		0.744	
MoCA	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	79	10.66 (6.97)	73	7.08 (6.44)
Week 8	67	10.48 (6.66)	44	7.43 (6.33)
Week 12	62	10.58 (6.90)	37	7.62 (7.03)
Mean change (95% CI)				
Baseline to Week 8	0.61 (−0.37; 1.60)		0.66 (−0.55; 1.86)	
Baseline to Week 12	0.62 (−0.43; 1.67)		0.26 (−1.06; 1.58)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.05 (−1.55; 1.46)		0.953	
Baseline to Week 12	0.36 (−1.28; 1.99)		0.671	
GAI	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	81	5.58 (5.70)	56	5.00 (5.32)
Week 8	65	5.95 (6.20)	26	3.38 (3.85)
Week 12	65	5.91 (6.20)	27	3.07 (3.09)
Mean change (95% CI)				
Baseline to Week 8	−0.78 (−1.69; 0.13)		0.91 (−0.49; 2.32)	
Baseline to Week 12	−0.35 (−1.26; 0.55)		1.27 (−0.11; 2.64)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−1.69 (−3.37; −0.01)		0.049	
Baseline to Week 12	−1.62 (−3.27; 0.03)		0.056	
PSMS	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	109	1.06 (1.31)	108	1.16 (1.29)
Week 8	101	1.14 (1.52)	98	1.19 (1.26)
Week 12	98	1.03 (1.38)	95	1.02 (1.17)
Mean change (95% CI)				
Baseline to Week 8	−0.04 (−0.17; 0.09)		0.00 (−0.14; 0.13)	
Baseline to Week 12	0.04 (−0.10; 0.17)		0.11 (−0.03; 0.25)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.04 (−0.22; 0.15)		0.710	
Baseline to Week 12	−0.07 (−0.26; 0.23)		0.444	
Charlson Comorbidity Index	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	108	2.54 (1.96)	101	2.57 (1.68)
Week 8	98	2.48 (1.84)	96	2.52 (1.65)
Week 12	94	2.50 (1.79)	93	2.57 (1.78)
Mean change (95% CI)				
Baseline to Week 8	0.04 (−0.09; 0.16)		0.04 (−0.08; 0.16)	
Baseline to Week 12	0.08 (−0.04; 0.20)		−0.04 (−0.16; 0.08)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−0.00 (−0.18; 0.17)		0.984	
Baseline to Week 12	0.12 (−0.05; 0.30)		0.169	
TUG	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	40	26.81 (16.67)	36	27.52 (20.36)
Week 8	25	64.84 (110.98)	20	36.22 (25.52)
Week 12	24	83.01 (136.12)	20	40.56 (26.94)
Mean change (95% CI)				
Baseline to Week 8	−35.95 (−66.04; −5.85)		−9.42 (−41.98; 23.14)	
Baseline to Week 12	−52.98 (−87.12; −18.83)		−17.10 (−53.39; 19.19)	
Difference in change	Mean (95% CI)		*p*-value	
Baseline to Week 8	−26.53 (−69.52; 16.46)		0.229	
Baseline to Week 12	−35.88 (−83.38; 11.63)		0.141	

Table 4. *Cont.*

	Control NHs	Intervention NHs
CDR	*n* (%)	*n* (%)
Baseline		
No/questionable cognitive impairment [c]	11 (10.7)	8 (7.7)
Mild cognitive impairment	30 (29.1)	20 (19.2)
Moderate cognitive impairment	28 (27.2)	32 (30.8)
Severe cognitive impairment	34 (33.0)	44 (42.3)
Week 8		
No/questionable cognitive impairment [c]	12 (12.6)	4 (4.3)
Mild cognitive impairment	24 (25.3)	8 (8.5)
Moderate cognitive impairment	28 (29.5)	34 (36.2)
Severe cognitive impairment	31 (32.6)	48 (51.1)
Week 12		
No/questionable cognitive impairment [c]	10 (11.1)	4 (4.3)
Mild cognitive impairment	23 (25.6)	10 (10.9)
Moderate cognitive impairment	26 (28.9)	28 (30.4)
Severe cognitive impairment	31 (34.4)	50 (54.3)
Odds of change (95% CI)		
Baseline to Week 8	0.97 (0.52; 1.83)	0.27 (0.14; 0.53)
Baseline to Week 12	0.68 (0.35; 1.30)	0.29 (0.14; 0.57)
Difference in change	OR (95% CI)	*p*-value
Baseline to Week 8	0.28 (0.11; 0.70)	0.007
Baseline to Week 12	0.42 (0.16; 1.09)	0.076
GMHR	*n* (%)	*n* (%)
Baseline		
Poor/Fair [c]	44 (41.5)	61 (61.6)
Good	37 (34.9)	19 (19.2)
Excellent	25 (23.6)	19 (19.2)
Week 8		
Poor/Fair [c]	43 (43.4)	57 (60.0)
Good	36 (36.4)	20 (21.1)
Excellent	20 (20.2)	18 (18.9)
Week 12		
Poor/Fair [c]	41 (42.7)	55 (60.4)
Good	41 (42.7)	17 (18.7)
Excellent	14 (14.6)	19 (20.9)
Odds of change (95% CI)		
Baseline to Week 8	1.22 (0.60; 2.44)	0.80 (0.35; 1.79)
Baseline to Week 12	1.57 (0.77; 3.20)	0.96 (0.42; 2.18)
Difference in change	OR (95% CI)	*p*-value
Baseline to Week 8	0.66 (0.22; 1.91)	0.440
Baseline to Week 12	0.61 (0.21; 1.81)	0.375

[a] A linear mixed model is used for continuous variables. A generalized linear mixed model is used for categorical variables. [b] NPI-subsyndromes are calculated as the sum of the following items: NPI-Agitation = Agitation + Disinhibition + Irritability; NPI-Psychosis = Delusions + Hallucinations; NPI-Affective = Depression + Anxiety. [c] Categories put together due to low *n* otherwise. CI, confidence interval; CDR, Clinical Dementia Rating scale; CSDD, Cornell Scale for Depression in Dementia; GAI, Geriatric Anxiety Inventory; GMHR, General Medical Health Rating Scale; MADRS, Montgomery and Asberg Depression Rating Scale; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; OR, odds ratio; PSMS, Physical Self-Maintenance Scale; QUALID, Quality of Life in Late-Stage Dementia; SD, standard deviation; TUG, timed "Up and Go" test.

Table 5. Analyses of secondary outcomes [a]: difference in change in medication prescriptions from baseline to Week 8/Week 12.

	Control NHs		Intervention NHs	
Total number of daily drugs	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	109	6.92 (3.49)	108	7.55 (3.04)
Week 8	102	6.73 (3.69)	99	7.14 (3.00)
Week 12	99	6.65 (3.54)	96	7.18 (3.16)
Mean change (95% CI)				
Baseline to Week 8		0.16 (−0.08; 0.39)		0.56 (0.32; 0.81)
Baseline to Week 12		0.30 (0.01; 0.58)		0.44 (0.16; 0.73)
Difference in change		Mean (95% CI)		*p*-value
Baseline to Week 8		−0.41 (−0.75; −0.06)		0.023
Baseline to Week 12		−0.15 (−0.58; 0.29)		0.504
Total number of PRN drugs	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	106	4.04 (2.74)	107	4.72 (2.89)
Week 8	96	4.42 (2.69)	97	4.48 (3.13)
Week 12	88	4.43 (2.78)	91	4.30 (3.12)
Mean change (95% CI)				
Baseline to Week 8		−0.26 (−0.56; 0.03)		0.11 (−0.18; 0.41)
Baseline to Week 12		−0.25 (−0.60; 0.09)		0.09 (−0.26; 0.43)
Difference in change		Mean (95% CI)		*p*-value
Baseline to Week 8		−0.38 (−0.80; 0.065)		0.083
Baseline to Week 12		−0.34 (−0.86; 0.17)		0.189
Antidepressants	*n*	*n* (%)	*n*	*n* (%)
Baseline	109	37 (33.9)	108	36 (33.3)
Week 8	102	35 (34,3)	99	30 (30.3)
Week 12	99	35 (35.4)	96	29 (30.2)
Odds for change (95% CI)				
Baseline to Week 8		1.00 (0.43; 2.33)		0.75 (0.34; 1.68)
Baseline to Week 12		1.04 (0.44; 2.42)		0.77 (0.34; 1.74)
Odds for difference in change		OR (95% CI)		*p*-value
Baseline to Week 8		0.75 (0.23; 2.40)		0.626
Baseline to Week 12		0.74 (0.23; 2.41)		0.623
Antipsychotics	*n*	*n* (%)	*n*	*n* (%)
Baseline	109	17 (15.6)	108	29 (26.9)
Week 8	102	14 (13.7)	99	25 (25.3)
Week 12	99	13 (13.1)	96	25 (26.0)
Odds for change (95% CI)				
Baseline to Week 8		0.70 (0.25; 1.98)		0.86 (0.37; 1.98)
Baseline to Week 12		0.67 (0.23; 1.93)		0.91 (0.39; 2.10)
Odds for difference in change		OR (95% CI)		*p*-value
Baseline to Week 8		1.23 (0.32; 4.65)		0.765
Baseline to Week 12		1.36 (0.35; 5.27)		0.654
Sedatives and hypnotics	*n*	*n* (%)	*n*	*n* (%)
Baseline	109	30 (27.5)	108	22 (20.4)
Week 8	102	26 (25.5)	99	21 (21.2)
Week 12	99	24 (24.2)	96	18 (18.8)
Odds for change (95% CI)				
Baseline to Week 8		0.81 (0.35; 1.90)		1.09 (0.43; 2.73)
Baseline to Week 12		0.80 (0.34; 1.89)		0.84 (0.32; 2.17)
Odds for difference in change		OR (95% CI)		*p*-value
Baseline to Week 8		1.33 (0.38; 4.67)		0.652
Baseline to Week 12		1.05 (0.29; 3.81)		0.942
Anxiolytics	*n*	*n* (%)	*n*	*n* (%)
Baseline	109	22 (20.2)	108	14 (13.0)
Week 8	102	20 (19.6)	99	12 (12.1)
Week 12	99	19 (19.2)	96	11 (11.5)
Odds for change (95% CI)				
Baseline to Week 8		0.94 (0.35; 2.51)		0.83 (0.27; 2.57)
Baseline to Week 12		0.85 (0.31; 2.28)		0.71 (0.22; 2.25)
Odds for difference in change		OR (95% CI)		*p*-value
Baseline to Week 8		0.89 (0.20; 3.93)		0.874
Baseline to Week 12		0.84 (0.18; 3.84)		0.822

Table 5. *Cont.*

	Control NHs		Intervention NHs	
Antidementia drugs	*n*	*n* (%)	*n*	*n* (%)
Baseline	109	9 (8.3)	108	34 (31.5)
Week 8	102	10 (9.8)	99	29 (29.3)
Week 12	99	11 (11.1)	96	29 (30.2)
Odds for change (95% CI)				
Baseline to Week 8		1.30 (0.36; 4.74)		0.80 (0.34; 1.89)
Baseline to Week 12		1.64 (0.46; 5.86)		0.83 (0.35; 1.95)
Odds for difference in change		OR (95% CI)		*p*-value
Baseline to Week 8		0.62 (0.13; 2.90)		0.541
Baseline to Week 12		0.51 (0.11; 2.35)		0.385

[a] A linear mixed model is used for continuous variables. A generalized linear mixed model is used for categorical variables. CI, confidence interval; OR, odds ratio; PRN, pro re nata; SD standard deviation.

Further, compared to the control group, participants in the iNHs had a statistically significant reduction in GAI score from BL to week 8 (−1.69 (−3.37; −0.01), $p = 0.049$), and a statistically significant reduction in the total amount of prescribed daily medications from BL to week 8 (−0.41 (−0.75; −0.06), $p = 0.023$). Residents in the iNHs, compared to residents in cNHs, had a significantly larger reduction in the odds of having a lower CDR score from baseline to week 8 ($p = 0.007$), but no significant difference in reduction from baseline to week 12.

4. Discussion

4.1. Brief Synopsis of Key Findings

This NH trial examined how an educational program on psychopharmacology and the use of NorGeP–NH in a real-world setting influenced QoL, other clinical outcomes, and medication prescriptions among NH residents. Our trial did not show any significant difference in change in QoL scores between iNHs and cNHs from BL to 12-week follow-up. Even though we found a statistically significant reduction in QoL among cNHs residents from BL to 12-week follow-up, this reduction was not relevant from a clinical perspective, according to what we assumed to be a clinically important reduction (33%). Our trial showed that the intervention did not reduce the total amount of daily prescribed drugs in the iNHs compared to cNHs after 12 weeks. However, there was a significant, yet temporary, reduction of the total amount of daily prescribed drugs from BL to 8 weeks, in the iNHs. Our results also showed that the depression score was significantly lower in the intervention group compared to the control group, at 12-week follow-up. Our trial did not show any significant difference between cNHs and iNHs in change for PTD category prescriptions.

4.2. Strengths and Limitations

A strength of this study is the fact that participants were assessed by healthcare personnel who worked in the NHs where the participants lived and who had good knowledge of the participants' clinical history. We also chose to focus on a "real-world" intervention performed by the same physicians treating the participants in the usual care setting, and not by conducting the intervention by external personnel, which has been previously discussed and has shown a possible lower adherence to suggested medication changes [22,25,26].

Another strength of our study is that NH personnel performed clinical evaluations with validated tools, commonly used both in Norway and internationally in NHs. This makes it easier to compare our results with other studies. In addition, only one investigator (first author) directed the intervention and follow-up assessments, and by having direct contact with every participating NH, the possibility of missing data in the dataset was minimized.

This study has several limitations. Participants were cluster-randomized to minimize within-NH contamination bias. Despite cluster-randomization, the intervention and control groups may have had differences that impacted the results. For example, at baseline, a

higher number of participants in the iNHs lived in special care units. This might reduce the potential beneficial effects of the performed intervention due to a higher level of morbidity in residents admitted to special care units, and, as a consequence of that, a lower QoL over time. Further, the short duration of the trial might not have been long enough to assess the long-term effects of the intervention. However, due to a high mortality rate in NHs [52], a shorter trial duration may reduce the number of people dropping out of the study.

Some assessment scores at BL, such as MoCA, QUALID, CSDD, GAI, or TUG, had several missing data. This may cause uncertainty when comparing the groups. We do not have an explanation for the reason why there were many missing data for QUALID or CSDD, as they are proxy-based assessment tools. For MoCA, GAI, and TUG, a possible explanation is that they require direct cooperation of the residents, which may have been difficult to achieve due to severe cognitive or physical impairment.

The data collectors were nursing home personnel, and they were blinded only during baseline data collection. This is a possible source of detection bias, as the assessors may have been influenced by the knowledge of randomization. However, most of the proxy-based assessment tools needed a deep knowledge of the participants and an observation time that lasted several days or weeks before an assessment was performed. Therefore, it would also be problematic to have the participants assessed by external, fully blinded personnel. Further, we did not analyze inter-rater reliability, and this may have led to bias in the data collection process, due to possible differences between data collectors. We did not collect precise data about how many nurses/authorized social workers participated in the data collection process, as this was decided internally in each nursing home ward. However, 42 wards participated in the study, and each ward had at least one or two data collectors. A large number of data collectors may also reduce a possible skewing of the distribution in the collected data.

Finally, we did not assess potential economic consequences of the intervention, which might be important to support such educational interventions in the future.

4.3. Considerations and Comparison with Relevant Studies

Our trial did not show a significant difference between the two groups in change in QoL. It is possible that our educational intervention, which focused on medication review and was only performed once, was not enough to improve QoL in the short term. In fact, a multicomponent, long-lasting intervention conducted in Norway showed no change in QoL during the first four months of intervention, but it showed an improvement nine months later [53]. However, our results are still in line with a Cochrane review conducted in 2016. That review analyzed the effect of different interventions to optimize drug prescriptions in NH residents and found no strong evidence showing intervention efficacy on resident-related outcomes, such as hospital admissions, mortality, adverse drug events, or QoL [16]. It is still important to note that even though we found no significant difference between the two groups in change in QoL, QoL did not worsen in the intervention group, while there was a significant reduction in QoL for participants in the cNHs. Indeed, the intervention might have prevented a possible worsening in QoL for the iNHs. However, the worsening in QUALID score we found in the control group may not be clinically relevant, as the mean (SD) score worsened from 21.31 (6.72) to 22.74 (7.64).

This trial showed a significant reduction in the total amount of prescribed drugs eight weeks after intervention, but not after 12 weeks. A possible explanation is that some drugs might have been reintroduced after a temporary discontinuation. However, we have not analyzed changes for all types of medication, as we only examined drug categories in the N05-/N06-ATC groups in detail. Our results seem to find partial support in previous studies. A recent systematic review showed that medication reviews can improve the appropriateness of drug prescription [17], which in some cases requires drug discontinuation. However, our trial may show that the effect of a medication review on the total medication amount is only temporary. The reduction in the total amount of drugs prescribed daily for older residents may have a beneficial effect on several clinical

factors, such as reduction of frailty, improvement in cognitive function, or lower risk of falls [2]. However, among the clinical outcomes examined in our trial, only depression improved after 12 weeks. On the one hand, depression is an important risk factor of polypharmacy and excessive polypharmacy [54]. On the other hand, several somatic prescription medications, such as antihypertensives, proton pump inhibitors, or analgesics, are known to possibly cause depression as an adverse outcome [55].

Residents living in iNHs showed an increase in CDR score during follow-up. A possible explanation might be that more participants in the iNHs lived in special care units, often offered to people with moderate to severe dementia symptoms and poor prognosis. This difference might also explain why at BL residents living in iNHs presented more severe cognitive symptoms measured by CDR and MoCA as well as more severe NPS measured by NPI-NH.

Even though a recent systematic review and meta-analysis showed that focused psychotropic medication review is effective in reducing PTD prescriptions in NH residents [22], our intervention used a more general drug chart review tool which is not PTD-specific, and this might explain why we did not find a significant difference in change in PTD prescriptions between the two groups. NorGeP–NH is described in a recent review as limitative, as it does not include possible inappropriate medications for specific comorbidities [56]. However, a newly performed multidisciplinary, long-term NH cluster-randomized intervention, using other drug review lists, also failed to show an effect in reducing PTD prescriptions [23].

5. Conclusions

Our intervention on the use of NorGeP–NH and on the correct use of PTD in older NH residents did not have an effect on QoL or PTD prescriptions in the short term. However, our intervention still showed a positive, yet temporary, effect on the total drug load residents received and on the level of depression. NorGeP–NH may still have value in clinical practice, even if the evidence of its beneficial clinical effects may be scarce. Future research on the use of NorGeP–NH and other medication review tools should be performed in NHs and in other clinical settings to assess their real effectiveness on medication prescriptions and on the overall health status of older adults.

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Institutional Review Board Statement: This trial was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the Regional Committee for Medical and Health Research Ethics (2017/2171 REK south-east D).

Informed Consent Statement: Every participant gave a written informed consent to be included in the trial. If participants had reduced capacity to consent, a written informed consent was obtained from the participant's next of kin.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author, but restrictions apply to the availability of these data. The data are not publicly available due to privacy or ethical restrictions. However, data may be available from the authors upon reasonable request and with permission of the Regional Committee for Medical and Health Research Ethics.

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Conflicts of Interest: G.S. has received honoraria for participating in a meeting of the Norwegian advisory board for Biogen regarding the aducanumab trials. The other named authors have no conflicts of interest, financial or otherwise.

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