Management of Pain and Burdensome Symptoms in Nursing Home Patients

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During my work as a nurse employed at the Department of Neurosurgery, Haukeland University Hospital, Bergen, I met patients with decreased or absent ability to self-report pain and burdensome symptoms caused by their cognitive impairment, cancer, cerebri, or a tracheotomy. These people were unable to describe their suffering and unpleasant feelings. Since that time, the assessment and treatment of pain and burdensome symptoms in people unable to give a valid self-report has been my main interest in practice and research.

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Content

Abbreviations

ADD	Assessment of Discomfort in Dementia
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical Classification System
ATE	Average Treatment Effect
CAMPAS-R	Cambridge Palliative Audit Schedule
CDR	Clinical Dementia Rating scale
CMSAS	Condensed Memorial Symptom Assessment Scale
CNPI	Checklist of Nonverbal Pain Indicators
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
DS-DAT	Discomfort Scale for Dementia of Alzheimer Type
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EOLD	End of Life in Dementia
EPCA-2	Elderly Caring Assessment 2
ESAS	Edmonton Symptom Assessment System
FACS	Facial Action Coding System
FAST	Functional Assessment Staging Tool
IASP	International Association for the Study of Pain
ICD-10	International Classification of Diseases, version 10
KPS	Karnofsky Performance Scale
MDASI	M. D. Anderson Symptom Inventory
MDS	Minimum Data Set
MMSE	Mini Mental State Examination
MOBID-2	Mobilisation-Observation-Behaviour-Intensity Dementia-2 Pain Scale
MSSE	Mini Suffering State Examination
NICE	The National Institute for Health and Care Excellence
NOPPAIN	Non-Communicative Patient' s Pain Assessment Instrument
NorPD	Norwegian Prescription Database
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti Inflammatory Drugs
PACSLAC	Pain Assessment Checklist for Seniors with Limited Ability to Communicate
PADE	Pain Assessment for the Dementing Elderly
PAINAD	Pain Assessment in Advanced Dementia
PAINE	Pain Assessment in Non-Communicative Elderly

PSMS	Physical Self Maintenance Scale
QoL	Quality of Life
RAI-PC	Resident Assessment Instrument for Palliative Care
RCT	Randomised Controlled Trial
REDIC	Resource use and Disease course in Dementia
SNAC-K	The National Study of Aging and Care – Kungsholmen
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic antidepressants
UN	United Nations
VAS	Visual Analogue Scale
WHO	World Health Organisation

List of publications

PAPER I   Sandvik, R., Selbaek, G., Seifert, R., Aarsland, D., Ballard, C, Corbett, C., Husebo, BS. Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: A cluster randomized trial. *Eur J Pain* 2014:18;1490-500.

PAPER II   Sandvik, R., Selbaek, G., Kirkevold, O., Aarsland, D., Husebo, BS. Analgesic prescribing patterns in Norwegian nursing homes from 2000 to 2011: trend analyses of four data samples. *Age Ageing* 2016:45;54-60.

PAPER III   Sandvik, R., Selbaek, G., Bergh, S., Aarsland, D., Husebo, BS. Signs of imminent dying and change in symptom intensity during pharmacological treatment in nursing home patients. A prospective trajectory study. *J Am Med Dir Assoc* 2016: 10.1016/j.jamda.2016.05.006.

Other publications not included in this thesis

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Husebo, BS., Ballard, C., Fritze, F., Sandvik, RK., Aarsland, D. 2014. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. *Int J Geriatr Psychiatry* 2014:29;828-36.

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Abstract

The assessment and treatment of pain and burdensome symptoms is a complex entity in elderly nursing home patients with and without dementia. This thesis aims to investigate the efficacy of individual pain treatment on pain intensity in people with advanced dementia, and to explore the prescribing patterns of scheduled analgesic drugs in Norwegian nursing homes. Further, the thesis explores the change in pain and symptom intensity during pharmacological treatment in nursing home patients who are dying and investigates whether it is possible to estimate the day of imminent death in such patients.

Three different studies provide data for this thesis. In Paper 1 we use data from a multicentre cluster randomised controlled trial (cRCT): "The Impact of Pain on Behavioural Disturbances in Patients with Moderate and Severe Dementia" (Pain-BPSD). Paper 2 is based on four data samples of scheduled analgesic drugs in Norwegian nursing homes between 2000 and 2011. For Paper 3, data are provided by a trajectory study entitled "Resource use and Disease Course in Dementia" (REDIC), that followed patients systematically from admission to a nursing home and over the course of three years or until death.

Aims

In Paper 1, we investigate the efficacy of a stepwise protocol of treating pain (SPTP) on pain intensity and Activities of Daily Living (ADL) in nursing home patients with moderate and severe dementia and behavioural disturbances.

In Paper 2, we explore the prescribing patterns of scheduled analgesic drugs in Norwegian nursing home patients between 2000 and 2011, examining associations with age, gender, cognitive function, and type of nursing home unit.

In Paper 3, we study signs of imminent dying and change in pain and symptom intensity during pharmacological treatment in nursing home patients, from the day a patient was perceived as dying to the day of death.

Methods

In <u>Paper 1</u>, we used secondary analyses from a 12-week cRCT including 352 patients with advanced dementia and behavioural disturbances from 18 nursing homes in Western Norway. The 60 clusters (single independent nursing home units) were randomised to intervention or control. Patients in the intervention group received individual treatment of pain with paracetamol (acetaminophen), morphine, buprenorphine transdermal system, and/or pregabalin. Participants who were randomised to the control groups received care as usual. The primary outcome measure was pain intensity assessed with the Mobilisation-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale. The secondary outcome measure was physical performance assessed by the Barthel ADL Index. Pain intensity scores were obtained from 327 patients (intervention n=164, control n=163) at four time points during the eight week intervention, with additional follow-up after a four-week wash-out period.

In <u>Paper 2</u>, we used secondary analyses of four nursing home samples (three observational studies and one cRCT) from 2000 (n=1926), 2004 (n=1163), 2009 (n=850), and 2011 (n=1858), representing 14 Norwegian counties. Scheduled analgesic prescriptions were extracted from medication records, and the following groups were applied: peripheral analgesics (paracetamol and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)), weak opioids (codeine and tramadol), strong opioids (morphine, fentanyl, oxycodone, and buprenorphine), and adjuvant therapy (pregabalin, gabapentin, and amitriptyline).

For <u>Paper 3,</u> we used data from a prospective, longitudinal trajectory trial including 607 patients from 47 Norwegian nursing homes during the first year after admission. We assessed the time between admission and the day of death, pain and burdensome symptoms, and pharmacological treatment during the last days and hours of life. Pain and burdensome symptoms were investigated using the Edmonton Symptom Assessment System (ESAS) and MOBID-2 Pain Scale. The level of dementia was assessed with the Clinical Dementia Rating scale (CDR), physical performance with Karnofsky Performance Scale (KPS), and Physical Self-Maintenance Scale (PSMS).

Nutrition and bedsores were assessed with the Resident Assessment Instrument for Palliative Care (RAI-PC).

Results

In <u>Paper 1</u>, we found that patients randomised to the intervention group conferred significant benefit from pain treatment on pain intensity compared with the control group at week 8 (P<0.001). After the four-week washout period between weeks 8 and 12, the pain intensity increased significantly. The overall ADL function did not improve by pain treatment. However, participants who were treated with paracetamol improved their ADL function after eight weeks (P=0.022).

In <u>Paper 2</u>, we reported a 65% increase of the analgesic drug prescription in Norwegian nursing homes between 2000 and 2011. The prescription of paracetamol and opioids increased by 113% and 118%, respectively. Strong opioids (fentanyl, buprenorphine, morphine, and oxycodone) increased almost nine-fold from 1.9% in 2000 to 17.9% in 2011 (P<0.001). Compared with individuals without dementia, people with dementia received fewer analgesics in 2000, 2004, and 2009, a difference we did not find in 2011.

In <u>Paper 3</u>, we showed that one in four patients died during the first year after nursing home admission. The identification of imminent dying was possible in 61% of the patients and was associated with increased fatigue and poor appetite. At the day of death, the administration of opioids, midazolam, and anticholinergic drugs increased significantly. The initiation of pharmacological treatment was associated with a reduction of pain intensity and symptoms such as anxiety. However, moderate and severe pain affected 60% of the patients on the day of imminent death, and was still high on the day of death (46%). Further, the prevalence of moderate and severe dyspnoea increased from 44% to 53% and death rattle from 8% to 19%, in the last days of life. Interestingly, respiratory symptoms such as dyspnoea and death rattle were not associated with the administration of opioids or anticholinergic drugs.

Conclusions

A stepwise protocol of treating pain (SPTP) improved the intensity of pain in people with dementia and those treated with paracetamol enhanced their ADL function.

Thus, it was substantial to find that the overall analgesic drug use increased from 35% to 58% in nursing home patients between 2000 and 2011 and that prescribing patterns were equal in patients with and without dementia in the 2011 sample. We suggest further that the identification of imminent dying may be challenging in nursing home patients and people with dementia, leading to a high symptom burden on the day of death. Respiratory symptoms in particular tend to increase towards the time of death. Our findings emphasise the necessity for staff education together with non-pharmacological and pharmacological interventions to improve the situation of elderly individuals who are dying.

This thesis mirrors the complexity of symptom assessment and treatment of pain and burdensome symptoms in our ageing population and highlights substantial needs for evidence-based implementation studies to investigate the efficacy of individual interventions in dying nursing home patients and people with dementia.

Sammendrag

Evaluering og behandling av smerte og belastende symptomer er utfordrende og komplekst hos eldre sykehjemspasienter og personer med demens. Denne avhandlingen undersøker om individuell smertebehandling reduserer smerteintensiteten hos personer med moderat til alvorlig grad av demens, samt studerer utviklingen av foreskrevet smertemedisin (analgetika) over tid i norske sykehjem. Videre undersøker avhandlingen endring i smerte- og symptombelastning ved medikamentell behandling hos døende sykehjemspasienter, og om tidspunktet for nært forestående død er mulig å estimere.

Datagrunnlaget for avhandlingen er hentet fra tre ulike studier. I artikkel 1 brukes data fra et multisenter klynge randomisert kontrollert studie (cRCT) "The Impact of Pain on Behavioural Disturbances in Patients with Moderate and Severe Dementia" (Pain-BPSD trial). Artikkel 2 anvender data fra fire utvalg av fast foreskrevet analgetika fra norske sykehjemspasienter fra 2000 til 2011. For artikkel 3 kommer data fra forløpsstudien "Resource Use and Disease Course in Dementia" (REDIC), som følger pasienter fra innleggelse i sykehjem og over tre år eller til personene dør.

Mål

I artikkel 1 undersøker vi om en stegvis protokoll for smertebehandling (SPTP) har påvirker smerteintensitet og aktiviteter i dagliglivet (ADL) hos sykehjemspasienter med moderat til alvorlig grad av demens og agitasjon.

I artikkel 2 studerer vi utviklingen av fast foreskrevet analgetika i norske sykehjem fra 2000 til 2011, og assosiasjoner til alder, kjønn, kognitiv funksjon og type sykehjemsavdeling (somatisk avdeling eller avdeling for personer med demens).

I artikkel 3 observerer vi mulige tegn på nært forestående død og endring i intensitet av smerte og andre belastende symptomer ved medikamentell behandling, blant annet bruk av analgetika, fra dagen en pasient ble vurdert som døende til dødsdagen.

Metode

I artikkel 1 ble det utført sekundære analyser fra et 12-ukers klynge randomisert kontrollert studie (cRCT). I alt ble 352 sykehjemspasienter med moderat til alvorlig grad av demens og agitasjon inkludert fra 18 sykehjem på Vestlandet. Seksti

sykehjemsavdelinger (1 avdeling=1 klynge) ble randomisert til enten intervensjons- eller kontrollgruppe. Pasienter i intervensjonsgruppen fikk individuell smertebehandling med paracetamol, morfin, buprenorphin depotplaster og/eller pregabalin. Personer randomisert til kontrollgruppen mottok sin sedvanlige pleie og omsorg. Hovedutfallsmålet var forandring i smerteintensitet og ble evaluert med Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) smerteskala. Sekundært utfallsmål var fysisk funksjon målt med Barthel ADL Index. Data for smerteintensitet forelå for 327 personer (intervensjon n=164, kontroll n=163), og ble vurdert ved fire tidspunkt gjennom den 8 uker lange intervensjonen, i tillegg ble det utført en måling i uke 12 etter en periode på fire uker med utvask av medikamentet.

I artikkel 2 ble det brukt sekundære analyser av fire sykehjemsutvalg (tre observasjonsstudier, og en cRCT) fra år 2000 (n=1926), 2004 (n=1163), 2009 (n=850) og 2011 (n=1858), i alt var 14 norske fylker representert.

Fast foreskrevet analgetika ble hentet fra medisinkort og gruppert slik; perifere analgetika (paracetamol og ikke-steroide antiinflammatoriske midler (NSAIDs)), svake opioider (codein og tramadol), sterke opioider (morfin, fentanyl, oxykodon og buprenorfin), og adjuvant terapi (pregabalin, gabapentin, og amitriptylin).

I artikkel 3 gjennomførte vi en prospektiv longitudinell forløpsstudie som fulgte 607 pasienter fra 47 norske sykehjem gjennom deres første år etter innleggelse. Vi kartla tiden fra dagen personen ble vurdert som døende og til dødsdagen, samt smerte og andre belastende symptomer, og medikamentell behandling som ble gitt i de siste timer og dager av livet. Symptomene ble evaluert med Edmonton Symptom Assessment System (ESAS) og MOBID-2 smerteskala. Grad av demens ble undersøkt med Klinisk Demens Vurdering (KDV), fysisk funksjon med Karnofsky Performance Scale (KPS) og Physical Self-Maintenance Scale (PSMS), ernæring og liggesår ble registrert ved hjelp av Resident Assessment Instrument for Palliative Care (RAI-PC).

Resultater

I artikkel 1 finner vi at en individuell og stegvis smertebehandling reduserer smerteintensiteten hos personer med demens. Etter en fire ukers utvask-periode fra uke 8 til uke 12 økte smerteintensiteten i intervensjonsgruppen signifikant. ADL

funksjonen viste ingen bedring eller forskjell mellom kontroll og intervensjonsgruppe, men personer som fikk paracetamol viste en økt ADL funksjon etter åtte uker (P=0.022).

I artikkel 2 viser vi at foreskriving av analgetika i norske sykehjem økte med 65 % fra 2000 til 2011. Foreskrivingen av paracetamol og opioider økte med henholdsvis 113 % og 118 %. Sterke opioider (fentanyl, buprenorphine, morfin og oxycodone) viste nesten en ni-dobling fra 1.9 % i 2000 til 17.9 % i 2011 (P<0.001). Sammenlignet med personer uten demens, hadde færre personer med demens foreskrevet analgetika i 2000, 2004 og 2009, denne forskjellen fant vi ikke i 2011.

I artikkel 3 viste vi at 1 av 4 av pasienter døde i løpet av deres første år etter innleggelse i sykehjem. Nært forestående død var mulig å estimere hos 61 % and pasientene, og var assosiert med redusert allmenntilstand (fatigue) og redusert appetitt. På dødsdagen økte administrasjonen av opioider, midazolam og antikolinerge legemidler signifikant. En oppstart av medikamentell behandling var assosiert med reduksjon av smerte og belastende symptomer som for eksempel angst. Likevel finner vi at moderat til alvorlig grad av smerte påvirket 60 % av personene da døden var nært forestående og var fremdeles høy på dødsdagen (46%). Videre fant vi at forekomsten av moderat til alvorlig grad av dyspné økte fra 44 % til 53 %, og dødsralling fra 8 % til 19 % i de siste timer og dager av livet. Symptomer fra respirasjonssystemet var ikke assosiert med administrasjon av opioider eller antikolinerge medikamenter.

Konklusjon

En stegvis protokoll for smertebehandling gir smertelindring for personer med demens og behandling med paracetamol øker ADL funksjonen. Det er således ett viktig funn at foreskriving av analgetika økte fra 35 % til 58 % bland sykehjemspasienter fra 2000 til 2011, og særlig at foreskrivingen av analgetika for dem som har og dem som ikke har demens er lik i 2011. Resultater fra artikkel 3 kan tyde på at det er utfordrende å identifisere når døden er nært forestående, noe som kan føre til at pasienten kan oppleve en høy symptombyrde på dødsdagen. Særlig gjelder dette økning av symptomer fra respirasjonssystemet. Våre funn understreker behovet for undervisning til personalet og implementering av medikamentell og ikke-

medikamentell behandling for å bedre situasjonen for sykehjemspasienter og personer med demens.

I tillegg til å gjenspeile kompleksiteten i evaluering og behandling av smerte og andre ubehagelige symptomer i vår aldrende befolkning, signaliserer denne avhandlingen behovet for kunnskapsbaserte implementeringsstudier som undersøker effekten av individuelle intervensjoner hos døende sykehjemspasienter og personer med demens.

1. Introduction

The global population is rapidly ageing, with substantial demographic changes the result of reduced birth numbers and mortality rates. An increased lifespan is expected globally because of better living conditions, fewer infections, and improved healthcare (WHO, 2012). The urbanisation of our societies makes the role of institutional care increasingly important for the aged, especially for elderly people living alone. One of the most important challenges is the care of people with chronic, age-related diseases, including those with cognitive impairment and dementia. In the last few decades, the number of people with dementia has increased to 35 million worldwide, and a doubling of this figure is expected during the next 30 years (Prince et al., 2013).

About 78,000 people are currently living with dementia in Norway. The rate is particularly alarming amongst those living in nursing homes, as over 80% have dementia (Helvik et al., 2015). The majority of these individuals have moderate to severe stages of dementia, and most have high needs for treatment and care related to impaired physical and cognitive function, lack of memory and speech, neuropsychiatric symptoms, and complex co-morbidities (Selbaek et al., 2013).

Advanced age is also associated with increased prevalence of pain often triggered by the musculoskeletal system such as fractures and neuropathies (Husebo et al., 2008). Recent documentation highlights that 40-60% of all nursing home patients are affected by daily pain (Achterberg et al., 2010, Husebo et al., 2011). People with moderate to severe dementia are no longer able to provide valid self-reports, and so best practice is for a caregiver (proxy-rater) with close knowledge of the person to evaluate the pain intensity by using a valid observational pain assessment instrument, before and after individual pain treatment has been initiated (Corbett et al., 2012). The assessment and treatment of pain in people with advanced dementia is complex, and earlier reports documented substantial differences between analgesic drug prescriptions in elderly people with dementia compared with younger counterparts without cognitive impairment.

In Norway, 40,000 people die every year (SSB, 2016b), despite efforts and policies to enable more people to die in the security of their home, almost 50% die in a nursing home, 32% die in a hospital, and only 7-15% at home (SSB, 2016b).

To improve advanced care planning and end-of-life care in nursing home patients with and without dementia, mid- and short-term prognostication as well as pain and symptom management are key tasks. Conferring to the newest guidelines of The National Institute for Health and Care Excellence (NICE), entitled "Care of dying adults in the last days of life", there is recognition of the fact identifying when someone is about to die is complex and so often goes unrecognised (NCCMH, 2015).
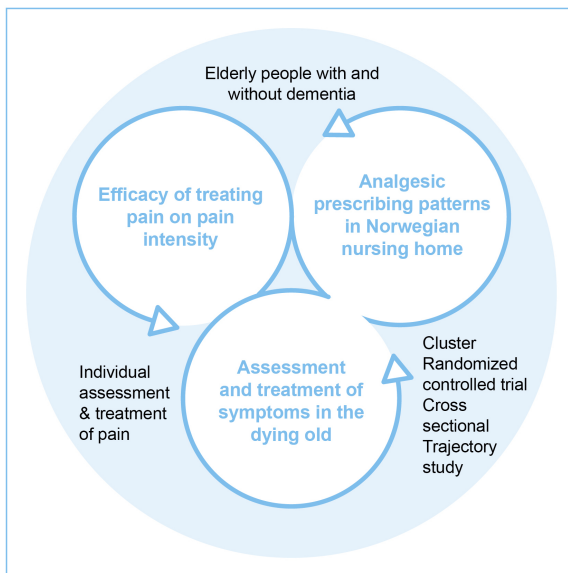
Figure 1. Complexity of assessment and treatment in nursing home patients

Proper and timely assessment and treatment of pain and burdensome symptoms in the last days and hours of life is challenged by methodological and ethical concerns. Only a few studies have undertaken the assessment and change in pain and symptom intensity alongside pharmacological treatment in a prospective design.

This thesis aims to explore the assessment and treatment of pain in people with dementia, the analgesic prescribing patterns over the last decade in Norway, and pain and symptom management at the end-of-life in Norwegian nursing home patients. As

demonstrated in Figure 1, we included different research samples, methods, and time points to establish this.

This thesis is comprised of three papers, and the PhD candidate, Reidun K. Sandvik, collected data for Papers 1 and 3, and for the 2009 sample in Paper 2. The candidate contributed to the study design of Papers 2 and 3, and wrote the manuscripts for the three papers. Whilst Reinhard Seifert performed the statistical analysis for Paper 1, the candidate was partly involved and conducted the statistical analysis for Paper 2 and 3.

2. Background

2.1 The ageing population

The development of the ageing population is caused by increasing life expectancy and the positive consequences of successes in the economy, welfare, and healthcare systems, both in the developed and in the developing world. Globally, the population is expected to have increased by 120% by 2050 from its figure in 1980. The proportion of persons 65 years and older will increase by 176%, from 6% in 1980 to 16% by 2050 (UN, 2015). Importantly, the significant a decline in mortality rates and rise in fertility rates hastens this process of demographic transition, particularly in Asia and Latin America (Prince et al., 2013). For the Western European countries, the development of the ageing population is also related to the post-World War II "baby boom" generation.

Consequently, these demographic developments are putting a considerable strain on the healthcare services. Healthcare expenditures are challenging to estimate in advance, but politicians suggest financial tasks should increase, especially for the elderly generation. According to national figures, most citizens 67 years and older live in their own home without any daily support, with s only 6% in this age group living in an institution. The situation changes for the age groups 80-89 years and ≥90 years where 18% and 37% live in a nursing home, respectively. This is reflected in the demographic details of the nursing home population, which suggest that the service is primarily used for the old individuals, most of whom are women.

2.1.1 Nursing home care

Currently, about 41,000 nursing home beds are available in Norway. Upon admission, patients have a mean age of 85 years, with more detailed proportions for different age groups (80-89 years (43%); 90+ years (34%); 67-79 years (18%), and < 66 years (5%)) (SSB, 2016b). The nursing home facility provides care for frail patients, and the mean length of survival from admission to death is two years (Vossius et al., 2015). The necessity for a place in a nursing home is often a

combination of moderate and severe care needs and mild to moderate dementia (SSB, 2016a).

The ageing population is the largest and fastest growing group in the healthcare system. Thus, the likelihood for dementia has increased significantly in the nursing home setting and today about 84% of residents have dementia (Helvik et al., 2015). Taking the demographic development into consideration, the required amount of nursing home beds for people with dementia is expected to almost quadruple during the next 30 years (Vossius et al., 2015). Dementia related challenges such as neuropsychiatric symptoms, sleep disturbances, and pain are important triggers for nursing home admission. In addition to the mental decline, nursing home patients experience a huge burden by multiple diagnoses (multi-morbidity=two diagnoses and more) such as stroke, cancer, and cardiovascular, lung, and neurological diseases. On average, each patient will have four different diagnoses and about 70% have five diagnoses or more (Graverholt et al., 2011). The overall load of these problems, including cognitive decline has a devastating impact on the activities of daily living (ADL) (Helvik et al., 2014).

2.2 Dementia

Dementia is a chronic, usually progressive and incurable disease, with increased risk of neuropsychiatric symptoms and mortality (Selbaek et al., 2014). The term "dementia" comprises a range of different, burdensome symptoms affecting cognition and the ability to perform daily activities.

A decline in cognitive functions such as memory, attention, problem solving, critical thinking, learning of new information, and orientation is most frequently described. In the later stages of the disease, the person loses his or her speech ability, and challenges such as incontinence, muscle stiffness, and balance problems are common (Edjolo et al., 2014). Most important for the person with dementia, their relatives, and also the nursing home staff are changes in the patient's usual behaviour and the development of behavioural disturbances (BPSD) or neuropsychiatric symptoms (NPS) such as agitation and aggression, depression, anxiety, irritability, delusion, hallucination, and sleep and eating disturbances (Prince et al., 2013). Due to the overall progressive nature of dementia, life expectancy is significantly reduced in these people (Wolfson et al., 2001, Sachs et al., 2011, Brodaty et al., 2012).

2.2.1 Prevalence of dementia

The current prevalence of dementia in people 60 years and older is 4%, worldwide, with regional differences ranging from 2% in Africa to 6% in North America (Ferri et al., 2005), and 7% in Western European countries (Prince et al., 2013). The prevalence of dementia is age-related, which means that about 2% in the 60-64 age group have dementia, a number that increases to 43% for those 90 years and older in Western European countries. During the next three decades, dementia prevalence will increase by 87% in Europe and 440% in Africa and Asia (Prince et al., 2013).

Despite this development, decreasing incidences of dementia have also been recently described in Western society (Jones and Greene, 2016). According to data from England collected between 1989 and 1994, the proportion of people with dementia was forecasted to be 8.3% in 2010. Repeated screening of the same area in 2008 demonstrated, unexpectedly, a 1.8 % decrease in prevalence to 6.5% (Matthews,

2013). This declining incidence of dementia is supported by an American study that calculated the five-year prevalence of dementia from 1977 to 2008, and was able to report a decrease in dementia incidence from 3.6% to 2% (Satizabal et al., 2016). Interestingly, Alzheimer's disease (AD) and vascular dementia were found to be reduced by 30% and 50% in Northern America, respectively (Satizabal et al., 2016), which the authors attribute to improved management of cardiovascular diseases and increased focus on lifestyle management, such as the reduction of stress and unhealthy eating, and increased activities. Although the evidence shows a decline in the incidence of dementia, the prevalence of individuals with dementia will rise due to a large and fast growing ageing population.

2.2.2 Different types of dementia disease

Diagnosis of dementia, including stage and type of dementia, is usually based on the International Classification of Diseases, version 10 (ICD-10) (WHO, 2015) and Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5 coding update) (APA, 2013). According to the ICD-10, dementia is possible when a person over a period of at least six months shows memory decline (especially for new information) and other cognitive functions, such as thinking and problem solving. This progressive syndrome causes decline in physical functioning and daily activities as well as social skills. Further, in persons with dementia, the awareness is preserved and the cognitive changes cannot be explained by depression or delirium. At least two of the following must be present: reduced ability to learn new skills, reduced ability in abstract thinking and reasoning, a decline in visuospatial function and language skills, and/or altered personality (Aarsland et al., 2011).

The physician Dr. Alois Alzheimer, was one of the first scientists who described AD with declined cognitive function and neuropsychiatric symptoms, and linked this to pathological findings in his famous patient, Auguste Deter (Alzheimer, 1907, Stelzmann et al., 1995). The detection of AD in 1906 was later confirmed by others and covers the largest group of neuro-degenerative brain diseases (Yen et al., 1987, Dickson et al., 1988). There is increasing evidence that AD is caused by plaques consisting of beta amyloid and neurofibrillary tangles. AD is a progressive disorder

with a preclinical stage, in addition to a mild, moderate, and severe stages. Together with Lewy bodies, Parkinson dementia, frontotemporal dementia, and Chorea Huntington, AD accounts for about 70 % of all dementia cases (Ott et al., 1995). The second largest group are people with vascular dementia (20%), caused by damage to blood vessels in the brain, which reduces the supply of nutrition and oxygen. Stroke caused by blood clotting or haemorrhage, or chronically damaged vessels after high blood pressure, diabetes or lupus are the main underlying diseases causing vascular dementia (Roman et al., 1993).

Less than 10% of dementia cases involve the disease as a secondary cause of another disease, such as brain trauma, cerebral cancer, vitamin insufficiency or infections.

In nursing home patients, comorbid AD and vascular dementia (mixed dementia) (Scherder et al., 2003b, Husebo et al., 2008, Perl, 2010) are most frequently observed. Mixed dementia is very common, and comprise about 50% of all cases (Jellinger and Attems, 2010).

2.2.3 Assessing stages of dementia

The first stage of dementia is mild, which involve increased memory loss, concentration problems, and reduced performance in instrumental ADL like social interactions and work performance. This evolves into moderate dementia, which constitutes a more severe impairment in memory, speech, and lower performance in instrumental ADL functions, and personal ADL like toileting and dressing might be affected. The final stage is severe dementia, in which extensive assistance in required for all ADL functions. At this stage, the person will have problems with speech, memory loss, and other cognitive functions.

In all stages neuropsychiatric symptoms such as delusions, hallucinations, and agitation can be seen (Bergh et al., 2011).

Over the last decades, a range of cognitive tests has been developed to screen for dementia or to evaluate cognition. The numerous amounts of instruments evaluate global cognitive function, or various specific cognitive aspects like attention, praxis or orientation, or the levels of dementia (Reisberg et al., 1997). Screening tools for

dementia, such as the Mini Mental State Examination (MMSE), must be able to discriminate between people with normal cognitive function and those with mild cognitive impairment or mild dementia (Folstein et al., 1975). Instruments to evaluate the severity of dementia used proxy rated information in addition to in depth knowledge of the person, both to screen for dementia and determine the stage of dementia. Commonly used such tools are the Clinical Dementia Rating Scale (CDR) or the Functional Assessment Staging Tool (FAST) (Hughes et al., 1982, Reisberg, 1988).

2.3 Pain

2.3.1 Pain components

Definition of pain

According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 2012). Pain is complex, and a multidimensional experience for the person who is living with the pain (Tracey and Dickenson, 2012). The reduction of verbal communication abilities does not ameliorate the experience of pain intensity, as stated clearly by the following: "The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment" (IASP, 2012).

Melzack and Casey (1968) suggest that the neurological pain pathways of pain perception are comprised by different pain systems: the sensory-discriminative (intensity, location, and quality of pain), the motivational-affective (emotional experience of pain, motivation, and pain affect), and the cognitive-evaluative (attention, anticipation, and memory) pain system (Melzack and Casey, 1968). These functions are related to the medial and lateral cerebral structures. In addition, an autonomic-endocrine system with the responsibility for stress reactions (Tsigos and Chrousos, 2002) and a central area for behavioural pain processes have been suggested (Monroe et al., 2012).

2.3.2 Pain types

Important for the clinician, there are two main types of pain: nociceptive and neuropathic pain. Nociceptive pain covers pain from the musculoskeletal system (somatic pain) and pain related to internal organs (visceral pain), whereas neuropathic pain is related to pain originating from the nervous system (Cherny and Portenoy, 1994).

Nociceptive pain

Somatic pain is caused by the nociceptive activation of the skin, muscles, and skeleton by diseases such as arthritis, fractures, skin conditions, or bursitis. Free nerve endings from large diameter myelinated Aδ fibres transmit a fast, sharp, and well-localised sensation to the spine via the dorsal root ganglion (Pasero and McCaffery, 1999). Elderly nursing home patients and people with dementia are especially affected by these conditions (Husebo et al., 2008), with 36% of home dwelling elderly people experiencing moderate to severe painful episodes (Cayea et al., 2006). The aging process dries the lumbar discs, causes arthritis, and osteoporosis, and leads to increases in tumours in the spine and muscle tissue (Jones et al., 2014). Studies from our group found that pain-related diagnoses of osteoporosis, fractures, and arthritis are most prevalent, affecting about 30% of the patients living in a nursing home (Husebo et al., 2008). The most frequent pain locations are related to the musculoskeletal system and especially hips, shoulders, and back (Husebo et al., 2010).

Visceral pain may originate from internal areas in the chest, abdomen, kidney or urinary bladder. Signals are transmitted via small diameter unmyelinated C-fibres transmitting dull, acing, and poorly localised signals (Pasero and McCaffery, 1999). Examples of painful conditions originating from the viscera are urine tract infections, ulcers, liver conditions, and irritable bowel syndrome (Moloney et al., 2015). In nursing home patients, nephrolithiasis, duodenal ulceration, or prostatitis may cause chronic or acute pain (Gloth, 2001). Investigations by our group demonstrate that 7% of nursing home patients have pain related to a skin/wound diagnosis, but twice as many have pain located in the skin (14%) (Husebo et al., 2008, Husebo et al., 2010). Although musculoskeletal pain is most frequently described, pain related to the urogenital organs (21%), abdomen (17%), and head/mouth/neck (16%) affects a substantial proportion of these individuals (Husebo et al., 2010). Notably, the prevalent numbers regarding orofacial pain are inconsistent, depending on age, aetiology, and setting investigated (Lipton et al., 1993, Riley and Gilbert, 2001). It is suggested that 40% of all older adults have pain in the oral cavity due to problems

such as infections or dry mouth caused by anticholinergic medication use (Jones et al., 2000, Toxopeus et al., 2014).

Neuropathic pain

The IASP states that neuropathic pain is caused by lesions or diseases of the somatosensory nervous system (Treede et al., 2008), which can be located in different origins and then referred to peripheral or central neuropathic pain. Peripheral neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" (Dworkin, 2012). Relevant diagnoses causing this type of pain are trauma to the first neuron, injury caused by damage to small vessels, and damage caused by chemotherapy or infection (Gilron et al., 2015). Diabetes related polyneuropathy or neuropathic pain in connection with the amputation of an extremity, are further causes of chronic pain. Central neuropathic pain is defined as "pain caused by a lesion or disease of the central somatosensory nervous system." A diagnosis of stroke, demyelination in connection with multiple scleroses, or Vitamin B_{12} myelopathy may cause central pain, especially in elderly people (Treede et al., 2008). The degeneration of spinal discs with related nerve compression or a cerebral tumour may also cause this type of pain.

2.3.3 Transmitters

A neurotransmitter is a chemical substance released by neurons as an impulse of information from one neuron to another or addressed to a muscle cell, organs, or other tissue. Typical pain transmitters are glutamate, substance P, calcitonin gene-related peptide, serotonin, and bradykinin (Latremoliere and Woolf, 2009).

2.3.4 Pain characteristics

The prerequisite for competent treatment of pain is proper assessment of the most typical pain characteristics: duration, location, quality, and intensity of pain.

Pain duration less than three months is defined as acute pain which serves to protect the body by the noxious stimuli of an injury, trauma, disease or surgery (Pasero and McCaffery, 1999). Chronic or persisting pain continues over time and may last many

years (Ready and Edwards, 1992). In chronic pain, the lack of meaningful function converts this state into an illness (Woolf et al., 2004).

Pain location identifies the source of pain and gives important information about the cause of the symptom or disease. This feature is mediated by the somatosensory cortex and a part of the lateral pain system. However, identification of pain location may be hampered by sensory inputs from different origins to the same nerve plexus, for example from the stomach to the heart region or the projection of pain (e.g., cholecystitis to the right shoulder) (Tucker et al., 2014).

Pain quality describes the patient's sensation of pain with words such as burning, itching, sickening, acing, throbbing, sharp, or others. This specification of quality alongside the location, history, and duration of pain are important elements that enable the initiation of appropriate treatment (Victor et al., 2008). Even with the same intensity and location of pain, the quality can differ and help distinguish between aetiologies.

Pain intensity is the most often assessed factor to describe the patient's pain experience, to initiate pain treatment, or to evaluate the efficacy of pain management. Pain perception in general is a complex interaction of different brain regions, already processed in early stages of the cerebral perception process (Iannetti et al., 2005). To measure the intensity of pain in cognitively intact people, self-rating instruments such the McGill Pain Scale (Melzack, 1975), Face Pain Scale (Hicks et al., 2001), Visual Analog Scale (VAS), or the Numeric Rating Scale (NRS) (Hawker et al., 2011) are usually used. The VAS is a line with two ends corresponding to no pain and severe pain. The NRS is an equivalent to the VAS with as an 11-point Likert scale ranging from 0 (no pain) to 10 (most severe pain).

2.3.5 Pain in nursing home patients and people with dementia

Reports of pain prevalence in nursing home settings have increased over the years, and show a considerable variation in their estimates of pain occurrence in this setting. For instance, Takai et al. (2010) performed a review and found that pain affects between 3.7% and 83% of patients (Takai et al., 2010). The vast variation might be associated to

differences in period of assessment, pain intensity assessed, procedures to collect the data institutional settings, stages of cognitive impairment, or simple staff competence (Zwakhalen et al., 2009, Takai et al., 2010, McAuliffe et al., 2012). To exemplify this, an investigation of excruciating pain found a prevalence of 3.7%, whereas a dichotomous investigation of pain /no pain found that 73% of the nursing home patients were in pain (Teno et al., 2004, Asghari et al., 2006). According to investigations using the Minimum Data Set (MDS) in European and North American nursing homes, pain presence varies from 32% in Italy to 65% in the United States (Achterberg et al., 2010, Shen et al., 2015).

Self-report of pain with validated pain assessment instruments are the "Gold standard" in pain assessment (Hawker et al. 2011). In people with mild dementia or mild cognitive impairment, self-report will also be the first choice (Hadjistavropoulos et al., 2014). In general, a valid self-report is more difficult to attain in people with moderate and severe dementia (MMSE total score <18) (Scherder et al., 2001, Lukas et al., 2013). However, other studies found that people with advanced dementia were able to judge their pain state (Closs et al., 2004, Zwakhalen et al., 2009).

Epidemiological studies report higher, lower, and the same prevalence of pain in people with and without dementia (Leong and Nuo, 2007, Shega et al., 2010, Docking et al., 2015, van Kooten et al., 2016). An important requirement in people with dementia is evaluation of their cognitive impairment using a tool like the MMSE, and to choose a validated pain assessment instrument accordingly. In 2008, the assessment of pain prevalence using such a validated observational pain behaviour instrument reported that about 60% of nursing home patients with dementia have mild to severe pain (Husebo et al., 2008).

2.3.6 Pain indicators in people with advanced dementia

Impaired language and abstract thinking puts older people with dementia at risk for under-treatment of their pain because of impaired self-report capacity (Hadjistavropoulos et al., 2014). Observation of the person's usual behaviour is key

when differentiating between behaviour that might be related to dementia and behaviour related to pain.

About 35 different observational pain behaviour instruments have been developed, validated, and reviewed in the literature during the last three decades (Corbett et al., 2012, Flo et al., 2014, Lichtner et al., 2014). Observation based pain instruments are used by a proxy-rater, usually the primary caregiver. These tools are mainly based on the observation of the patients' typical behaviour, which possibly is changed as a reaction when experiencing pain. The American Geriatric Society Panel (AGS-Panel) described typical pain behaviours expressed by people with dementia (Table 1) (AGS-Panel, 2002, Hadjistavropoulos et al., 2014).

Table 1. Behaviours related to pain in persons with dementia as described by the AGS Panel.

Pain behaviour	Example of behaviour
Facial expression	Grimacing, brow lowering, mouth opening, closing eyes
Verbalization, vocalization	Moaning, groaning, crying, complaining
Body movements	Pulling away, rubbing, freezing, limping, clenched fists
Change in interpersonal interactions	Aggressive, affect, combative, resisting care, difficult to console
Changes in activity patterns/routines	Wandering, appetite change, sleep disturbances
Mental status changes	Crying, confusion

Despite this essential progress, there are still considerable challenges to assess pain in people with dementia because proxy-rating and judgment by others has to replace self-report procedures of pain intensity, pain affect, pain quality, pain location, patient history (duration of pain), and physiological changes. In people with advanced dementia, the assessment of observed pain behaviour can simply be a suggestion as it cannot guarantee the actual pain state, and can never be as valid as a self-report.

In addition, most older adults (>90%) experience chronic pain that they have adapted to, and will therefore avoid painful movements (pain avoidance effect) (Vlaeyen and Linton, 2012). Pain related to the musculoskeletal system appears through standardised guided movements, whereas pain related to the internal organs, head, and skin is more hidden and difficult to quantify (Husebo et al., 2007).

2.3.7 Observational pain behaviour instruments

To our knowledge, the first tool developed and tested to assess pain behaviour in people with dementia was the Facial Action Coding System (FACS) (Ekman and Friesen, 1978). The instrument evaluates anatomical features of the patient's face during induced pain stimulus and categorises reactions in different units of the face. By means of the FACS, it has been shown that people with dementia have even more facial reactions compared with those without cognitive impairment (Kunz et al., 2009). Since the development of the FACS in 1978, scientists and clinicians have worked constantly at the development of new approaches, resulting in a number of different types of pain tools currently being available. In Table 2 below we list the 12 most promising pain instruments according to a recent review (Husebo et al., 2012).

However, it is noteworthy that not all these instruments are tested in relation to all aspects of validity and reliability, and only few fulfil the newest recommendations by the consensus-based standards for the selection of health measurement instruments (COSMIN) group, including psychometric properties of responsiveness (Mokkink et al., 2006, Angst, 2011). Although the scales are widely used, basic elements like instructions for staff education and how to interpret the results are not always established, affecting the feasibility of the scales.

Responsiveness of observational pain behaviour instruments
According to the COSMIN protocol, responsiveness is defined as the "ability of an instrument to detect change over time in the construct to be measured" (Mokkink et al., 2010). Until now, seven of the 35 observational pain assessment instruments for people with dementia have been tested for responsiveness in four studies (Husebo et al., 2016). Morello et al. (2007) explored the psychometric properties of the Elderly Pain Caring Assessment 2 (EPCA-2), which rates the pain intensity in non-communicating elderly people by eight behavioural items with two dimensions: the signs outside and during caregiving (Morello et al., 2007). Cohen-Mansfield (2008) conducted an open pain treatment trial and highlighted the PAINE and PADE pain tools to be most responsive to assess the change in pain intensity scores (Cohen-Mansfield and Lipson, 2008). In the third study by Rat et al., they conducted an open

pain treatment trial to investigate the responsiveness of the acute pain instrument, Algoplus® (Rat et al., 2011). These studies are important contributions to evaluate the efficacy of pain treatment and change in pain intensity after pain treatment has been initiated. However, methodological issues flaw them, some studies are underpowered or lack a power calculation, thy have a high drop-out rate, or no control group to compare changes over time with the intervention groups (Husebo et al., 2014b). Our own group investigated the responsiveness of the MOBID-2 Pain Scale, using data from a cluster randomized clinical trial that included 352 Norwegian nursing home patients with moderate and severe dementia and agitation (Husebo et al., 2011). In this study, we followed the latest COSMIN recommendations and found the MOBID-2 Pain Scale to be responsive to change (Husebo et al., 2014b).

Table 2. The most promising pain assessment instruments for people with advanced dementia.

First author	Pain assessment instruments	Target and tool items	Scoring
Abbey et al. (2004)	Abbey Pain Scale	Acute and chronic pain. Vocalisations, facial expression, change in body behaviour, behavioural change, physiological change, physical change.	A continuous scale is broken down over four intensities; no pain (0-2), mild pain (3-7), moderate pain (8-13) and severe pain (14+).
Kovach et al. (1999)	Assessment of Discomfort in Dementia (ADD)	Pain, affective discomfort, discomfort. Facial expression, mood, body language, voice, behaviour.	No intensity scoring. The ADD has a five step protocol for intervention.
Feldt (2000) and Nygaard and Jarland (2006)*	Checklist of Nonverbal Pain Indicators (CNPI)*	Acute pain. Nonverbal vocalization, facial grimacing, bracing, rubbing, restlessness, vocal complaints.	Each item is scored dichotomously as no (0) and yes (1), thereafter the scores are added. Pain is assessed at rest and on movement separately
Hurley and Volicer (2001)	Discomfort Scale for Dementia of Alzheimer Type (DS-DAT)	Discomfort. Noisy breathing, negative vocalisation, facial expression (content, sad, frightened), frowning, body (relaxed, tense), restlessness.	Each item is scored dichotomously as present/not present. Items designated as present are scored for frequency, duration and intensity using VAS scales.
Lefebvre-Chapiro (2001) and Hølen et al. (2005)*	DOLOPLUS-2*	Chronic pain. The sub scales of somatic reactions (e.g., complaints, protecting body parts, sleep); psychomotor reactions (e.g., mobility), and psychosocial reactions (e.g., social life, communications), in total 10 items.	Each item of the three scales is rated on a severity scale from 0-3, and added to a total score from 0-30. A score of 5 indicates pain.
Morello et al. (2007)	Elderly Caring Assessment 2 (EPCA-2)	Pain intensity. Observations before care of facial expression, posture, movement in and out of bed, social interaction, and signs during care of anxiety, reactions to care, reactions to body movement, complaints vocalised.	Each items is rated on a scale from 0-4 for intensity.
Husebo et al. (2010)	MOBID-2 Pain Scale*	Chronic pain. Two parts; musculoskeletal pain investigated during five standardised movements and observation of face, vocalisation and defence. Visceral pain and pain from head and skin assessed by five items.	Ten items are scored on an 11-point NRS scale from 0-10 for intensity. The total score is a separate NRS from 0-10. The tool also contains a body sketch.

Snow et al. (2004)	Non-Communicative Patient's Pain Assessment Instrument (NOPPAIN)	Chronic pain. Four sections; questions about care giving, pain behaviours, location of pain using a body drawing, verbal descriptor scale from no pain to unbearable pain to assess intensity.	Each item is scored on a dichotomous as scale for present (1) or absent (0), and added to a total score.
Fuchs-Lacelle and Hadjistavropoulos (2004)	Pain Assessment Checklist Seniors Limited Ability to Communicate (PACSLAC)	Acute and chronic pain. All 60 items are divided into four subscales: facial expressions, body movements, social interaction and physiological indicators.	There is a mix of multiple choices and intensity scoring. No total score.
Villanueva et al. (2003)	Pain Assessment for the Dementing Elderly (PADE)	Pain and/or distress. In all 24 items are divided into three parts; physical, global assessment, and ADL.	Each item is scored from 0-2, and the sum is added to a total score from 0-10.
Warden et al. (2003)	Pain Assessment in Advanced Dementia (PAINAD)	Pain severity. Berating, negative vocalisation, facial expression, body language, ability to be console.	
Cohen-Mansfield (2006)	Pain Assessment in Non-Communicative Elderly (PAINE)	Pain severity. All 22 items assess facial expressions, verbalisation, body movement, change in routines, and visible cues.	Each item is scored on a severity score from 1 (never) to 7 (several times an hour). No total score.

* Norwegian translation available

2.4 Pain management

2.4.1 Analgesics

Medical drugs are classified by the Anatomical Therapeutic Chemical Classification System (ATC) (WHO, 2011). Analgesic drugs are covered by the ATC-system N02 for analgesics and M01 for NSAIDs. Adjuvant therapies with for instance N03A antiepileptics (gabapentin and pregabalin) or N06AA for tricyclic antidepressants (TCA) cover drugs that have primary indications other than pain relief but may also be affective in case of neuropathic pain.

The primary classes of analgesics are divided into peripheral and central acting drugs also demonstrated by the Pain Treatment Ladder developed by the World Health Organisation's (WHO, 2016a) (Figure 2):

ADJUVANT THERAPY

Anti-depressants
Anti-epileptics
Capsaicin
Muscle relaxant
Nerve blocks
Steroids

STRONG OPIOIDS

STEP 3
Buprenorphine
Fentanyl
Hydromorphone
Ketobemidone
Methadone
Morphine
Oxycontin
Pethidine

WEAK OPIOIDS

STEP 2
Codeine
Tramadol

NON-OPIOIDS

STEP 1
Non-Steroid Anti-Inflammatory drugs (NSAIDs)
Paracetamol (acetaminophen)
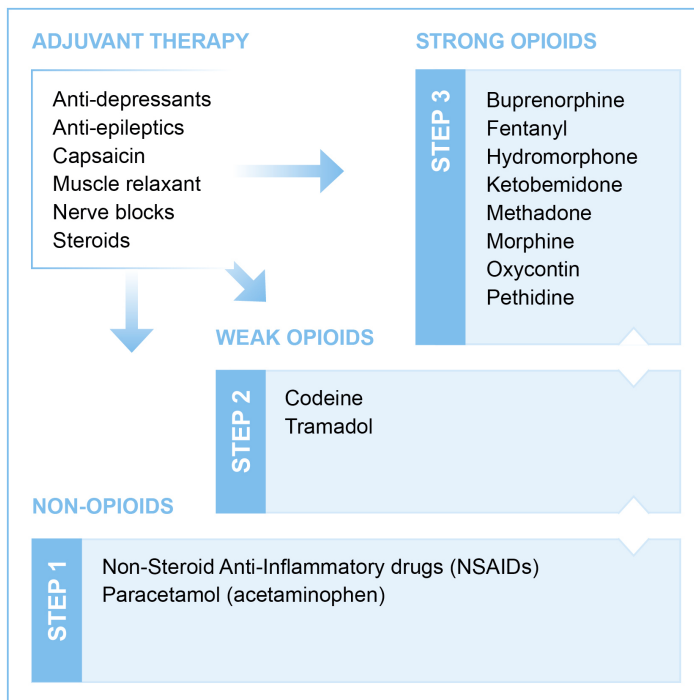
Figure 2. Pain Treatment Ladder according to the WHO

2.4.2 Pain treatment recommendations

Currently, several practice recommendations for the treatment of pain in elderly people are available. A non-systematic literature search revealed eight guidelines and position statements on pharmacological pain management for older adults and long-term care patients (Table 3). Pain treatment guidelines for people with dementia are not yet available, although a recent systematic review exists on the efficacy of analgesic drugs on pain intensity in persons with dementia (Husebo et al., 2016). The authors conclude that there is weak evidence on analgesic drugs used in persons with dementia due to small and underpowered studies with no randomisation a and lack of adequate pain assessment tools (Husebo et al., 2016). We have provided a range of recommendations based on the guidelines that can be found in Appendix 1, Table 4.

Table 3. Clinical guidelines for pharmacological treatment in older adults

| Guideline	Author
Long term care	
Pain in residential aged care facilities. Management strategies	APS (2005)
Pain management in the long-term care setting	AMDA (2012)
Older adults	
The management of persistent pain in older persons	AGS-Panel (2002)
Pharmacological management of persistent pain in older persons	AGS-Panel (2009)
Multidisciplinary guideline 'Recognition and treatment of chronic pain in vulnerable elderly people	Achterberg et al. (2012)
Guidance on the management of pain in older people	Abdulla et al. (2013)
Position statements	
Transforming long-term care pain management in North America: the policy-clinical interface	Hadjistavropoulos et al. (2009)
Position statement 21: Pain in older people	ANZSGM (2012)
Identifying and Managing Pain in People with Alzheimer´s Disease and Other Types of Dementia: A Systematic Review	Husebo et al. (2016)

2.4.3 Analgesic drug prescription in Norway

Analgesic drug use in the general population

During the last decade, the overall consumption of analgesic medication did not change in Norway. We analysed numbers from the Norwegian Prescription Database (NorPD) and found the proportion of analgesic drug (ATC N02+M01) users to be 30% in 2004 and 32% in 2014 (NorPD, 2016). However, the proportion of daily-dispensed doses increased by 23% between 2004 and 2014. Although the overall proportion of persons prescribed analgesics may be unchanged in recent years, the proportion of dispensed paracetamol increased from 3% to 8%, whereas NSAID prescribed declined from 18% to 16% in this period. The proportion of persons using opioids (ATC N02A) increased slightly from 9% to 10.5%, and whilst the prescription of morphine and fentanyl remained stable from 2004 to 2014, the prescription of oxycodone and buprenorphine increased fivefold from 0.1 to 0.6%, and 0.05 to 0.3%, respectively.

The increased consumption of opioids in the general population of Norway is consistent with findings from a population-based study of opioid prescription rates in people with cancer and non-cancer pain, using data from the NorPD (Fredheim et al., 2010). Non-cancer pain is increasingly managed by tramadol, buprenorphine, and oxycodone. The use of morphine and fentanyl remains stable but the use of codeine has slightly decreased for non-cancer pain (Fredheim et al., 2013).

Figure 3 demonstrates the analgesic drug prescription for elderly people 75 years and older, based on the NorPD data in 2014. We find that the proportion of individuals using paracetamol and buprenorphine increases with age, whereas NSAIDs are less frequently prescribed as age increases (NorPD, 2016).
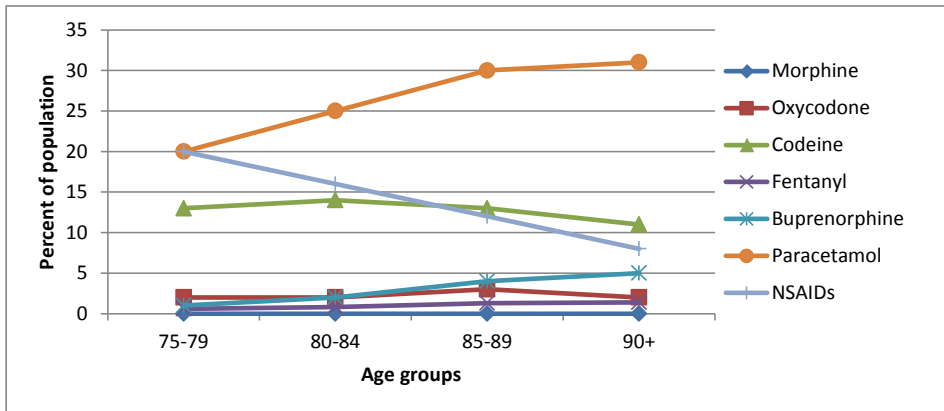
Figure 3. Proportion of prescribed analgesics drugs in Norway (2014) displayed by age categories according to data from the Norwegian Prescription Database (NorPD)

2.4.4 Analgesic drug prescription in nursing home patients and people with dementia

Over 20 years ago, Ferrell et al. demonstrated the vast pain intensity experienced by nursing home patients and the under-prescription of analgesic agents in people with dementia (Ferrell et al., 1990, Ferrell, 1995). Since then, under-treatment of pain has been documented in different countries and settings (Scherder and Bouma, 1997, Allen et al., 2003, Nygaard et al., 2003, Closs et al., 2004, Nygaard and Jarland, 2005, Achterberg et al., 2007, Reynolds et al., 2008, De Souto Barreto et al., 2013).

Analgesic drugs are more extensively prescribed to nursing home patients compared with age matched home-dwelling people, particularly paracetamol and opioids (Haasum et al., 2011, Johnell and Fastbom, 2012, Jensen-Dahm et al., 2014). However, NSAIDs are more usual in home-dwelling older adults possibly because they are available over the counter (Haasum et al., 2011, Johnell and Fastbom, 2012).

Most analgesic prescription studies in nursing home patients do not report the patients' pain intensity scores or the potential pain relieving effect alongside the prescription numbers. A Dutch study including 350 nursing home patients investigated residents at baseline and after six months in regards to pain intensity and analgesic consumption. The pain intensity was recorded on an ordinal scale as no, mild, and severe, and the analgesics used were categorised as paracetamol, NSAIDs,

opioids, and others. Although individuals with severe pain received more opioids and more combination therapy, this study found that severe pain after six months was associated with baseline pain (OR 18.55, 95% CI 5.19–66.31). This result may indicate that pain treatment was not adapted fully to the individuals' pain intensity, especially since fewer than 45% of the residents received any analgesics despite having pain (Smalbrugge et al., 2007).

Analgesic prescribing patterns seems to be influenced by level of dementia. Despite the same painful diagnoses, more persons without and with mild dementia were administered analgesics compared with those suffering from moderate and severe dementia (Closs et al., 2004). Reynolds et al. (2008) also included persons without dementia and those with mild, moderate, and severe dementia, finding that individuals with no or mild dementia were prescribed an analgesic drug more often than people with moderate and severe dementia. Interestingly, analgesic drugs given as needed and nonpharmacological interventions seem to be stable across groups (Reynolds et al., 2008).

Morrison et al. (2000) demonstrated that people with dementia after hip fracture surgery did not receive the same amount of analgesic drug prescription compared with patients without dementia (Morrison and Siu, 2000). New evidence suggests that an equal proportion of persons with and without dementia receive paracetamol and opioids after hip surgery, although people with dementia receive lower doses of opioids at day one and two after surgery compared with older adults without dementia (Jensen-Dahm et al., 2016).

In general, we find that Nordic studies report an increase of analgesic drug prescriptions in the elderly and people with dementia. In Finland, for instance, the prescription of paracetamol increased from 34% to 47%, opioids from 12% to 23%, and adjuvant therapy from 1% to 5%, between 2003 and 2011. Especially, the use of strong opioids increased from 2% to 14% in this period (Pitkala et al., 2015).

A Swedish study of home-dwelling and nursing home patients aged 85 years and older, demonstrated that those with dementia were treated more frequently with paracetamol compared with people without dementia, whereas the amount of opioids

was similar in both groups (Lovheim et al., 2008). Another study from Sweden, the National Study of Aging and Care – Kungsholmen (SNAC-K), found that people with dementia were more often treated with both paracetamol and opioids. Even after adjusting for painrelated diagnoses, dementia, age, sex, and setting, the likelihood for analgesic drug use was significantly increased in those with dementia compared to others (Haasum et al., 2011).

Comparable trends are observed in a Danish study that explores the opioid drug prescriptions (Jensen-Dahm et al., 2014) of elderly people living at home or in a nursing home. Home-dwelling people with dementia were found to receive more analgesics compared with persons without dementia. In nursing homes, it was discovered that opioids are slightly less often prescribed in people with dementia compared with people with no dementia (35% vs 43%). Strong opioids were found to be equally prescribed between the groups: buprenorphine was more often used in people with dementia (12.3%) compared with persons without dementia (9.5%) (Jensen-Dahm et al., 2014).

2.4.5 Efficacy of treating pain on pain intensity in people with dementia

Despite the increasing analgesic drug use in nursing home patients and people with dementia, there remains a considerable dearth of studies that evaluate the effects of analgesic drugs on pain intensity in these people (Flo et al., 2014). Until now, only few studies investigate the efficacy of treating pain on neuropsychiatric behaviour or pain intensity (Pieper et al., 2013, Husebo et al., 2016). Currently, only two prospective studies with more than 10 participants are available using a validated pain assessment instrument to assess the efficacy of analgesic drugs on pain intensity (Buffum et al., 2004, Husebo et al., 2011). So far, the evidence finds that paracetamol (acetaminophen) can be recommended for the treatment of pain in people with dementia in doses as high as 3g/day (Buffum et al., 2004, Chibnall et al., 2005), and that morphine is effective for people with dementia when the doses are individualised (Manfredi et al., 2003).

2.5 End-of-life care in the nursing home

In Norway, about 19,000 people or 48% of the dying population pass away in a nursing home (SSB, 2016b). This implies that most of the patients admitted to a nursing home will also die in this setting. In the last days and hours of their lives, nursing home patients may experience pain and burdensome symptoms that require proper end-of-life care and treatment. Most of these people will have dementia with a mean length of survival between five and nine years (range 1 to 16 years) (Davies et al., 2004). Our own REDIC report demonstrates a mean survival rate of eight years (Vossius et al., 2015).

Dementia is a progressive and life limiting disease that requires proper treatment and care with high focus on quality of life (QoL) (van der Steen et al., 2014). The WHO defines end-of-life care (palliative care) as the "approach to improve the QoL of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment the treatment of pain and burdensome symptoms" (WHO, 2016b).

Whereas the principles of palliative care are well established in dying cancer patients (Black et al., 2011), such care remains under-studied and not yet available for dying nursing home patients and people with dementia. One important prerequisite for dignified dying is the staff's ability to identify the end-of-life and the day of imminent dying (Mitchell et al., 2009). Recognising dying is vital in order to provide individual treatment, communication, and ethical decision making (NCCMH, 2015).

In people with dementia, one of the main challenges may be the lack of active feedback regarding effects and side effects of the treatment. Additionally, reduced consciousness and delirium may impair the self-report capacity. A relevant answer may be the identification of typical symptoms that characterise a three- to six-month mortality risk or symptoms unique to imminent death. Pneumonia (41%), repeated episodes of fever (53%), and eating problems (86%) have been related to an increased six-month mortality risk in people with dementia (Mitchell et al., 2009), and other

symptoms such as breathlessness and dyspnoea (46C), pain (39%), and pressure ulcers (39%) are characteristic of the last three months of life (Mitchell et al., 2009).

Preparing communication and Advance Care Planning

Advance Care Planning (ACP) involves health care plans by preparing communication and necessary decisions for future treatment and care. Unfortunately, nursing home patients and people with dementia are often poorly informed and less included in ACP (Forbes et al., 2000). When important decisions need to be taken, the central person will no longer be able to participate in important ethical decisions, and thus cannot be asked about their preferences, values, and choices. This can lead to unfortunate and random decisions. As such, the inclusion of the patient, relatives, and health care workers (including the responsible physician) should be initiated before the patient is unable to communicate their own preferences (Flo et al., 2016).

2.5.1 Cancer care versus dementia care in the dying

ACP, ethical decision making, and the proper assessment and treatment of pain and burdensome symptoms are the hallmarks of dignified end-of-life care in dying people (Flo et al., 2016, van der Steen et al., 2014). These approaches are widely developed, tested and described in the literature in people with cancer (Theis et al., 2007). The newest NICE guidelines review the emerging literature and provide evidence-based recommendations to ameliorate the suffering in the dying adult (NCCMH, 2015). The document also underlines the importance of identifying imminent death as a prerequisite to initiating changes in treatment regimes, communication, and up-start with pain and symptom management. The evaluation of these actions, especially the efficacy of the medication on pain and burdensome symptoms, are highlighted by the NICE guideline.

Although these procedures are implemented and routinely used on palliative care wards and in hospices and hospital units, end-of-life care for dying elderly people and those with dementia are less developed, implemented, and tested. Indeed, the NICE guidelines did not find one single randomised control trial or prospective study of a high quality that included nursing home patients or people with dementia (NCCMH, 2015).

Our current knowledge, developed by research and clinical experiences related to palliative care for cancer patients cannot easily be transferred to nursing home patients and people with dementia (van der Steen et al., 2014), because whilst they may die in the same setting, people with dementia die differently than patients with cancer. Data derived from the MDS comparing 1609 dying people with dementia and 883 patients dying from cancer in nursing homes reported significantly more burdensome interventions used in the former patient group, including feeding tubes, blood tests, and restraints used during the 120 days before death (Mitchell et al., 2004). Another smaller comparison between patients on a palliative care ward in a nursing home and usual nursing home patients with multi-morbid nursing home patients who suffer from cardiovascular diseases, degenerative skeletal illnesses, and neurological complaints, including dementia, demonstrates relevant differences. Cancer patients are often younger, cognitively intact, and prepared for death as a result of participation in communication and ethical decisions over a longer time period (Husebø et al., 2004). They also received pain and symptom management, which is vital in this critical period of life.

2.5.2 Assessment and treatment of pain and burdensome symptoms in the nursing home

In general, the main burdensome symptoms in dying patients are pain, dyspnoea, anxiety, delirium, and death rattle (Chang et al., 2000). It has been suggested that the occurrence of these symptoms is common among the vast majority of all dying patients (Husebø et al., 2004). In the palliative care setting these challenges can be sufficiently relieved by subcutaneous application of morphine, scopolamine/robinul, haloperidol, and midazolam (Sutton et al., 2003). It has been suggested that acute heart failure enhances sensations of dyspnoea, death rattle, and suffocation, thus increasing the need for morphine as the only effective treatment in the final hours of life (Twycross, 1997). Importantly, these observations are less investigated prospectively in the elderly. To our knowledge, only a few studies explore palliative care in nursing home patients and people with dementia (Brandt et al., 2005a, Brandt

et al., 2005b, Brandt et al., 2006a, Brandt et al., 2006b, Mitchell et al., 2009, Hendriks et al., 2014, Klapwijk et al., 2014, Hendriks et al., 2015).

Four reports have been provided by the same underlying study, investigating different aspects in end-of-life care for dying nursing home patients (Brandt et al., 2005a, Brandt et al., 2005b, Brandt et al., 2006a, Brandt et al., 2006b). In all, 516 Dutch nursing home patients were included by a nursing home physician when life expectancy was suggested to be less than six weeks. Main symptoms providing this prognosis were little or no fluid intake (43%), fatigue (32%), and little or no appetite (25%) (Brandt et al., 2005a).

The prediction of survival in nursing home patients is challenging and depends on close knowledge of the person (Brandt et al., 2006b). In this sample, 91% died within the estimated six weeks, with median survival of three days. An accurate prediction of survival was possible when death occurred within seven days and estimated to 93%, thereafter the accuracy dropped to 16% (Brandt et al., 2006b). A smaller selection of 463 patients of the same sample was investigated for burdensome symptoms in their last 48 hours, and showed a reduction in pain and burdensome symptoms towards death. Within two weeks after the patient died, the nursing home physician assessed the patient's symptom burden for two time periods; 48-24 hours before death, and 24-0 hours before death using the ESAS tool and the Resident Assessment Instrument for Palliative Care (RAI-PC). Although they found an amelioration of symptoms, the burden is still high during the last 24 hours of life as shortness of breath (23%), pain (22%), anxiety (21%), and nausea (17%) affect the person to a substantial degree on the day they die (Brandt et al., 2006a).

Another Dutch observational study included 36 patients expected to die within the next seven days (Klapwijk et al., 2014). Twelve died before any assessments were made, which left 24 patients. Two nursing home physicians performed all the assessments no longer than two weeks after the patients died using the Mini Suffering State Examination (MSSE), the PAINAD, the DS-DAT, and the End of Life in Dementia scales-Comfort Assessment in Dying (EOLD-CAD). The different tools found different severities of symptom burdens, with the MSSE evaluating patients 11

times in seven days and reported 35.5% to be in pain, whereas the EOLD-CAD investigated pain six times, and found pain present in 15% of the assessments. Further, they found that all patients received morphine in their last week of life (Klapwijk et al., 2014).

Another Dutch study was performed and reported in two different papers (Hendriks et al., 2014), both of which focused on the prevalence of pain, dyspnoea, and agitation, along with the treatment provided to the symptoms investigated. The study followed 372 patients with dementia from admission to a nursing home, 218 of whom died during follow-up; the nursing home physician was able to complete a retrospective assessment of 213 of these individuals. In addition, 119 retrospective assessments from eligible patients were added, with 330 patients in total. The first paper reports on symptom severity and treatment provided in the last week of life in dying nursing home patients with dementia (Hendriks et al., 2014). This study found higher intensity scores compared with previous studies, with pain affecting 52% of individuals in the last week of life, and dyspnoea and agitation affected 35% of the patients. The symptom severity did not differ with dementia severity in this study. Pain was most frequently addressed using opioids (67%), paracetamol (60%), and NSAIDs (17%).

The second paper reports on the longitudinal follow-up with assessments every six months over 3.5 years (Hendriks et al., 2015), and found that in the last week of life, 78% patients suffered pain, 52% had dyspnoea, and 35% were agitated. Further, this study found that parenteral opioid drug use was increasingly provided for pain (61%), whereas morphine (69%) and oxygen (40%) were increasingly used to treat dyspnoea, and nonpharmacological interventions (50%), anxiolytics (62%), and antipsychotics (44%) were increasingly used to treat agitation in dying patients with dementia in their last week of life. The assessment of the three symptoms was dichotomised, which might be the reason for the higher symptom prevalence found in this study.

2.5.3 End-of-life care assessment instruments

Several instruments are available to explore different aspects of end-of-life care in the nursing home and relatives' and caregivers' satisfaction with the care, quality of death and dying, and the prediction of death (van Soest-Poortvliet et al., 2012). We only discuss assessment tools related to symptom management, and a brief description of relevant tools is presented in Table 5, Appendix 2.

The Edmonton Symptom Assessment System (ESAS) includes nine different items for pain and symptoms (pain, fatigue, nausea, appetite, depression, anxiety, dyspnoea, drowsiness, and well-being), validated by severity scores on an 11-point Likert scale (0 = not present, 10 = as bad as possible) (Bruera et al., 1991). The ESAS instrument has been validated for validity and reliability in a range of settings, such as palliative care units, hospitals, and nursing homes (Nekolaichuk et al., 2008). It has also been validated for proxy-rating (Pautex et al., 2003, Nekolaichuk et al., 1999a, Nekolaichuk et al., 1999b), in people with dementia (Yang et al., 2016), and in dying nursing home patients (Brandt et al., 2006a). However, ESAS is not validated in dying nursing home patients with dementia.

The most complete and frequently used assessment instrument is the RAI-PC with 15 domains of symptoms, physical and mental status, communication, and administrative items (Steel et al., 2003). The RAI-PC has a dichotomous scoring system for absence and presence of each symptom, which, however, may reduce the feasibility to assess treatment efficacy. The tool is validated in several languages and it is available in Norwegian (Steindal et al., 2014).

3. Aims of the thesis

3.1.1 General aims

This thesis investigates the efficacy of individual pain treatment on pain intensity in people with advanced dementia, and explores the prescribing patterns of scheduled analgesic drugs in Norwegian nursing homes. Also, the thesis explores the change in pain and symptom intensity during pharmacological treatment in dying nursing home patients.

3.1.2 Specific aims

Paper 1

To investigate the efficacy of a stepwise protocol for treating pain on pain intensity and ADL in nursing home patients with moderate and severe dementia and agitation.

Paper 2

To explore the prescribing patterns of scheduled analgesic drug use in Norwegian nursing home patients from 2000 to 2011, with the association with age, gender, cognitive function, and type of nursing home unit.

Paper 3

To examine whether it is possible to determine signs of imminent dying and to investigate the change in pain and symptom intensity during pharmacological treatment in nursing home patients, from the day a patient was perceived as dying to the day of death.

4. Methods

4.1.1 Paper 1

Design

We conducted secondary analysis from data derived from the Pain-BPSD Study entitled "Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: Cluster randomised clinical trial" (Husebo et al., 2011). This was a cRCT investigating the effects of a stepwise protocol for treating pain (SPTP) over eight weeks, with an additional four-week wash out period. All patients were followed regularly with defined primary and secondary outcome measures at baseline and weeks 2, 4, 8, and 12.

Setting and participants

In all, 352 nursing home patients with advanced dementia and agitation representing 60 clusters or units from 18 nursing homes located in five municipalities in Western Norway were included. One nursing home unit was defined as one cluster to prevent crossover contamination from the intervention to the control group. Nursing home units were allocated randomly by a statistician to either their usual care (N=177) or to the SPTP (N=175). For this secondary analysis, we included patients with a pain intensity score assessed by MOBID-2 Pain Scale at baseline (N=327), allocated to the control (N=163) or intervention (N=164) group.

Eligibility criteria

Patients could be included if they were 65 years or older, showing severe agitation (Cohen-Mansfield Agitation Inventory (CMAI)≥39), and had moderate or severe stages of dementia according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) and Functional Assessment Staging Tool score ≥ 4. Patients were excluded if they had a severe mental health disorder, had been resident in the nursing home≤ four weeks, had an expected survival ≤ six weeks, or had a known allergy to the study medication.

Primary and secondary outcome measures

All assessment scales can be found in Table 6, Appendix 3. The primary outcome measure was the MOBID-2 Pain Scale, an observational pain assessment tool administered by nursing staff. Pain is assessed in two parts containing a total of 10 items related to the musculoskeletal system and internal organs, head and skin. The assessment of pain intensity is based on observed pain behaviour related to vocalisation, facial expression, and defensive body positions. Musculoskeletal pain is assessed during five standardised guided movements (part 1 of the MOBID-2) performed during morning care. As an example, this comprises the movement of the hands, shoulders, back, legs, and torso. In addition, five items of visceral pain are recorded by staff observation over time (part 2 of the MOBID-2). Further, a body drawing for pain location is available. Each item is evaluated on a 10-point Likert scale for pain intensity (range 0-10). Based on all information, an independent overall 10-point numeric rating scale is completed. The MOBID-2 Pain Scale is tested regarding validity, reliability, and responsiveness (Husebo et al., 2007, Husebo et al., 2009, Husebo et al., 2010) and indicates no or mild pain (range 0-2), moderate pain (range 3-6), and severe pain (range 7-10).

A secondary outcome measure was personal ADL (P-ADL) assessed with the Barthel ADL Index. This tool ranges from 0-20, with lower scores indicating higher dependence in ADL functions on ten items (eating, bathing, grooming, dressing, bowel function, continence, toileting, transfer from bed to chair, mobility and stair use) (Mahoney and Barthel, 1965).

The screening tool used to assess cognitive function was the Mini-Mental State Examination (MMSE), a 30-point interview administered by the research nurse or staff in which a higher score means better cognitive function. Cognitive skills covered by the instrument include orientation, recall, calculation, memory (short and long term), language, executive function, and visuospatial function. After initial development and testing, the tool has proven to be sensitive, valid, and reliable, including in later validations (Folstein et al., 1975, Pangman et al., 2000), and has been tested for nursing home patients in Norwegian (Engedal et al., 1988). In addition, we assessed the level of dementia using the Functional Assessment Staging

(FAST) ranges from no dementia to severe dementia (1/2=no dementia; 3= mild; 4/5 = moderate; 6/7 = severe) (Reisberg, 1988).

Intervention

Patients assigned to step 1 were treated with oral paracetamol 3 g/day (Table 7). If this was already provided at baseline, patients were allocated to step 2 (oral morphine, maximum 20 mg/day). If swallowing problems were present, patients were allocated to step 3, which was buprenorphine transdermal patch (maximum 10 μg/h). Persons with neuropathic pain started on step 4 (oral pregabalin, maximum 300 mg/day) (Table 7). In general, the treatment was individual and based on the individual's ongoing pain management at baseline; if needed, different analgesics could be combined.

Table 7. Stepwise protocol for the treatment of pain

Step	Pain treatment at baseline	Study medication	Doses	N=164 (%)
1	No analgesics, or low dose of paracetamol	Paracetamol	3g/d	112 (68)
2	Full dose of paracetamol, or low dose of morphine	Morphine	5mg x 2/d-10 mg x 2/d	3 (2)
3	Low dose of buprenorphine or inability to swallow	Buprenorphine patch	5μg/h-10μg/h	37 (23)
4	Neuropathic pain	Pregabalin	25mg x 1/d-300mg/d	12 (7)

Statistics

We calculated the mean, standard deviation, and range for participant demographics. The differences between groups were tested with two-sample independent t-tests for normally distributed continuous variables. Categorical variables showing normal distribution were analysed by proportion of sample size and the chi-square test. Non-normally distributed categorical variables were analysed using the Mann–Whitney U test.

Further, we investigated the mean and standard error of the MOBID-2 Pain Scale and Barthel ADL Index scores over time between groups with linear random intercept quantile mixed effects models, using the nursing home as nestling level.

The statistical significances of the p-values were considered as follows: highly significant (P<0.001), significant (P<0.005), and moderately significant (P<0.05).

The statistical analyses were conducted with IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY), R version 3.0.0 (The R Foundation for Statistical Computing, Vienna, Austria), and package nlme-3.1-109.

Ethics

Verbal and written informed consent was obtained directly in conversations with cognitively intact nursing home patients. If a patient was not able to consent on his or her own behalf, verbal and written informed consent was obtained in direct conversation with the patient (if possible) and his or her next of kin or legal guardian.

The study was registered by ClinicalTrials.gov number NCT01021696 and the Norwegian Medicines Agency (EudraCT nr: 2008-007490-20). It was further approved by the Regional Committee for Medical Ethics, Western Norway (REK-Vest 248.08) in accordance with the local law.

4.1.2 Paper 2

Design

Trend analysis of analgesic drug prescriptions in four study samples.

Setting and participants

In Paper 2 we extracted information from medication records of scheduled medication from four different studies sampled in 2000, 2004, 2009, and 2011.

The first sample from 2000 investigated the association between the use of constraints and patient and nursing home unit characteristics (Kirkevold et al., 2004). In all, this study included 1926 patients representing 222 nursing home units from 54 municipalities in Norway. The patients included were sampled from regular somatic wards (160 wards, 1362 patients) and special care units (91 wards, 564 patients) to ensure those with dementia were included. Between March and November 2000, 12 specially-trained research nurses asked the patients' primary caregivers about the suffering the patients experienced during their last seven days of life.

Data from the second sample were collected in 2004 and derived from a study exploring the prevalence of NPS in people with various stages of dementia, and the association between NPS and psychotropic drug use (Selbaek et al., 2007). The data included 1163 patients from 26 small, medium, and large nursing homes, representing 18 municipalities and four counties. Structured interviews with the patients' primary caregivers were conducted by 16 registered nurses who had completed a two-day training course on dementia and neuropsychiatric symptom assessment.

The 2009 sample was the screening data for the Pain-BPSD study containing 850 patients from 18 nursing homes in Western Norway. This study is further presented in Paper 1.

The fourth sample (2011) is a follow-up of the study performed in 2004. In 2011, 25 of the 26 nursing homes were investigated repeatedly, and 41 new nursing homes were added. In all, 1858 patients were examined, including the 99 patients who were investigated in both the 2004 and 2011 samples.

Outcome variables

We collected the demographic variables age and gender, and also obtained the type of ward, level of dementia (using the Clinical Dementia Rating (CDR) or FAST), and the patients' diagnoses. The CDR assesses level of dementia on six domains (memory, orientation, reasoning, social activities, instrumental, and personal activities), each assessed from 0-3, with a total sum of boxes ranging from 0-18. The total score of the CDR is calculated based on an algorithm giving precedence to memory. This total score ranges from no dementia to severe dementia (0=no dementia; 0.5=very mild; 1=mild; 2=moderate; 3=severe). The CDR shows valid psychometric properties and is widely used in the nursing home setting (Hughes et al., 1982, Selbaek et al., 2008). Furthermore, it is also available in Norwegian. The FAST situates the level of dementia on a seven-point scale from no dementia (1) to severe dementia (7). The FAST also show good psychometric validation and is widely used in Norwegian. In our study, dementia was defined as CDR$\geq$1, and FAST>3 (Reisberg, 2006).

We coded the medication according to the ATC system and divided analgesics into meaningful groups: peripheral analgesics (paracetamol and NSAIDs), weak opioids (codeine and tramadol), strong opioids (morphine, fentanyl, buprenorphine, and oxycodone), and adjuvant therapy (pregabalin, gabapentin, and amitriptyline). The ATC codes used were as follows: any analgesic (N02), paracetamol (N02BE01), NSAIDs (M01A-H), codeine (N02AA59), tramadol (N02AX02), morphine (N02AA01), fentanyl (N02AB03), buprenorphine (N02AE01), oxycodone (N02AA05), pregabalin (N03AX16), gabapentin (N03AX12), and amitriptyline (N06AA09).

Statistics

We calculated the mean, standard deviation, and range for participant demographics. The differences between groups were tested with two-sample independent t-tests for normally distributed continuous variables. Categorical variables showing normal distribution were analysed by proportion of sample size and the chi-square test. We used mixed-model multivariate regression with the nursing home as the nesting level to investigate prescribing patterns. We also used logistic regression to understand the impact of sample year on the analgesic prescription.

Statistical significance of the p-values were considered as follows: highly significant ($P<0.001$), significant ($P<0.005$), and moderately significant $P<0.05$.

The statistical analyses were conducted with IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY) and STATA/IC 13.1

Ethics

In 2000, 2004, and 2011 patients and their next of kin were informed about the study design and their possibility to withdraw from inclusion and at any stage of the study. In accordance with local law, ethical approval was granted by the Regional Committee for Medical Ethics, South and East Norway (REK-South/East) for 2004 (61-04001) and 2011 (2010/1894). The 2009 sample was registered at ClinicalTrials.gov (NCT01021696), and approved by the Norwegian Medicines Agency (EudraCT nr: 2008-007490-20) and the REK-Vest South and East Norway (REK-South/East) for 2004 (61-04001) and 2011 (2010/1894). The 2009 sample was

registered at ClinicalTrials.gov (NCT01021696), and approved by the Norwegian Medicines Agency (EudraCT nr: 2008-007490-20) and the REK-Vest (248.08).

4.1.3 Paper 3

Design

We use data from the Resource Use and Disease Course in Dementia Trial (REDIC). This is an ongoing trajectory study (2012-2017) including four cohorts: 1. Home-dwelling older adults aged ≥70 years who receive domiciliary care (N=1000); 2. Healthy older adults living at home aged ≥70 years (N=300); 3. Nursing home patients aged ≥65 years or younger if admitted with diagnoses of dementia (N=691), and 4. Patients aged ≥65 years and admitted to a memory clinic (N=300).

Baseline assessment was performed within four weeks after admission to a nursing home. At day of imminent death and day of death, the patient's primary caregiver called the responsible research nurse at the day when the patients were suggested to be imminent dying and at the day of death. The assessment was carried out as an interview based on the last 24 hours. We included the medication administered in the last 24 hours as regular prescriptions and medication administered "as needed".

Setting and participants

This paper uses data from the nursing home cohort where patients were followed from admission (baseline) and with assessments every 6 months for 3 years or until death. In all, 47 nursing homes were included from Hedmark (7 nursing homes, 43 nursing home units), Oppland (22 nursing homes, 88 nursing home units), Nord-Trøndelag (13 nursing homes, 26 nursing home units) and Bergen (5 nursing homes, 25 nursing home units).

Eligibility criteria

Patients were eligible for inclusion if newly admitted to a nursing home and 65 years or older, or young and with a diagnosis of dementia. We excluded persons with a life expectancy less than 6 weeks.

Outcome variables

The pharmacological treatment was grouped as follows: opioids (weak and strong), anticholinergic drugs (morphine-scopolamine, scopoderm, glycopyrronium bromide), antiemetic drugs (metoclopramide, odansetron and haloperidol), anxiolytic/sedatives (benzodiazepines and derivates). The ATC codes used were opioids (N02A), anticholinergic drugs (A03AB/A04AD/N02AG01), antiemetic drugs (A04AA/N05AD01) and anxiolytic/sedatives (N05BA/N05CD08).

Assessment scales

To assess the patients` ADL function, we included the PSMS scale which comprises of six domains such as toileting, eating, dressing, grooming, transfer, and bathing. The PSMS scale ranges from 6-30, increasing score means increasing dependence in daily functioning (Lawton and Brody, 1969). Physical function was also assessed using the KPS, which is a staging of function from normal (100) to dead (0) in 11 steps (Vincent, 1984) (Crooks et al., 1991).

Burdensome symptoms at the end-of-life were assessed using the Edmonton Symptom Assessment System including nine symptoms. At end-of-life six relevant items for the end-of-life not included in the ESAS was extracted from the Resident Assessment Instrument- Palliative Care (RAI-PC) (sleep quality, vomiting, delirium, agitation, death rattle, and constipation).

Statistical analyses

We calculated the mean, standard deviation and range for participant demographics. The differences between groups were tested with two-sample independent t-tests for normally distributed continuous variables. Categorical variables showing normal distribution were analysed by proportion of sample size and the chi-square test. Non-normally distributed categorical variables were analysed using the Mann–Whitney U test.

Further, we examined the differences between groups and over time with regression models for repeated measurements with random intercept effects, linear mixed model for continuous and multilevel logistic regression for dichotomous outcome variables.

Statistical significance of the p-values were considered as follows; highly significant (P<0.001), significant (P<0.005), and moderately significant (P<0.05).

Statistical analyses were conducted with IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY) and STATA/IC14.

Ethical aspects

Verbal and written informed consent was obtained directly in conversations with cognitively intact nursing home patients. If a patient was not able to consent on his or her own behalf, verbal and written informed consent was obtained in direct conversation with the patient (if possible) and from his or her next of kin or legal guardian.

The REDIC study is registered at ClinicalTrials.gov, number NCT01920100 and approved by the REK-ØST (2011/1738).

5. Main results

Paper 1

Sandvik, R., Selbaek, G., Seifert, R., Aarsland, D., Ballard, C, Corbett, C., Husebo, BS. Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: A cluster randomized trial. *Eur J Pain* **2014:18;1490-500.**

- At baseline, >70% of the participants had at least one pain related diagnosis.
- Assessed using the MOBID-2 Pain Scale, 80% (n=282) had a total pain intensity score of >1 and 62% (n=203) ≥3.
- Patients suspected of suffering from neuropathic pain had higher pain intensity scores (MOBID-2 Pain Scale mean 6.1, P=0.001) compared with patients with musculoskeletal pain (MOBID-2 Pain Scale mean 3.65) at baseline.
- Individual treatment of pain following a SPTP led to significant improvements to the pain intensity compared with the control group, after two weeks (average treatment effect (ATE) -0.703, SE 0.24, P=0.004). The effect continued to week 8, comprising a 45% changeover time and between groups (ATE=-1.393, SE 0.3, P<0.001).
- The use of paracetamol ameliorated the pain intensity at week 2 (ATE=-0.67, P=0.010), week 4 (ATE=-0.92, P<0.001), and week 8 (ATE=-1.30, P<0.001).
- Treatment with buprenorphine transdermal system and extended release morphine reduced the pain intensity scores in week 8 (ATE=-1.14, P=0.008).
- Pregabalin had a conferred effect, showing a total pain intensity reduction of 64% from week 0 to week 8 (ATE=-3.53, P<0.001).
- Compared with the control, the ADL function did improve in the intervention group (week 8, P=0.443). However, patients receiving paracetamol demonstrated improved ADL function from baseline to week 8, compared with the control group (ATE=+1.00, P=0.022).

Paper 2

Sandvik, R., Selbaek, G., Kirkevold, O., Aarsland, D., Husebo, BS.Analgesic prescribing patterns in Norwegian nursing homes from 2000 to 2011: trend analyses of four data samples. *Age Ageing* **2016:45;54-60.**

- Between 2000 and 2011, the analgesic drug prescriptions increased from 35% to 58% in Norwegian nursing homes.

- Paracetamol was most commonly prescribed and increased from 23% to 48%, followed by opioids (11% to 24%) and adjuvant therapy (1% to 4%).

- The use of strong opioids (morphine, buprenorphine, oxycodone, and fentanyl) increased almost nine-fold from 2% to 18%.

- The prescription of NSAIDs decreased from 7% in 2000 to 3% in 2011 (P<0.001).

- Women received more analgesics than men in all age groups: <80 (P<0.001), 81–90 (P=0.001), and 91+ (P<0.001).

- Prescription of analgesic drugs increased with age.

- The proportion of patients prescribed concomitant analgesics increased from 3% to 5% for paracetamol and weak opioids, respectively, between 2000 and 2011 (P<0.001).

- The prescription of any analgesic drug was significantly related to the absence of dementia in the 2000 (P=0.028), 2004 (P=0.027), and 2009 samples (P=0.011), but this was not found in 2011 (P=0.737).

Paper 3

Sandvik, R., Selbaek, G., Bergh, S., Aarsland, D., Husebo, BS. Signs of imminent dying and change in symptom intensity during pharmacological treatment in nursing home patients. A prospective trajectory study. *J Am Med Dir Assoc* 2016: 10.1016/j.jamda.2016.05.006.

- One in four newly admitted nursing home patients died during the first year.

- Patients who died during the first year had more severe dementia (P=0.006), high dependency (P<0.001), pain in the mouth (P=0.003), nutritional substitutes (P=0.006), bedsores (P=0.008), and more severe symptoms of dyspnoea (P<0.001), drowsiness (P=0.001), fatigue (P=0.001), less well-being (P=0.025), and reduced appetite (P=0.003) compared with those who survived the first year after admission.

- Staff members were able to identify the day of imminent dying in 61% of the patients by signs of increased fatigue (OR 1.8, 95% CI 1.16; 2.85, P=0.009) and poor appetite (OR 1.2, 95% CI 1.06; 1.41, P=0.005).

- From the day of imminent dying to the day of death, the administration of weak opioids (3.7% vs. 37.3%, P<0.001), anticholinergic agents (6.2% vs. 18.6%, P<0.001), midazolam (8.6% vs. 17.2%, P<0.001), and strong opioids (48.1% vs. 65.7%, P<0.001) increased significantly.

- Between the day of imminent dying and the day of death, the prevalence of several symptoms decreased, such as pain (60% vs. 46%, P<0.001), low sleep quality (50% vs. 38.2, P<0.001), anxiety (44% vs. 31%, P<0.001), depression (33% vs. 15%, P<0.001), nausea (24% vs. 12%, P<0.001), constipation (24% vs. 8%, P<0.001), and delirium (16% vs. 3.1%, P<0.001).

- Despite declining symptom severity, patients still experienced pain (46%), sleep problems (40%), and anxiety (31%) on the day of death.

- Respiratory symptoms such as dyspnoea (44% vs.53%, P=0.040) and death rattle (8 vs. 19%, P<0.001) increased significantly during the last days of life.

- Initiation of opioids was associated with the reduction of pain (P=0.041) but it was not related to dyspnoea.

6. Discussion

We live in a very particular death-denying society. We isolate both the dying and the old, and it serves a purpose. They are reminders of our own mortality. We should not institutionalize people. We can give families more help with home care and visiting nurses, giving the families and the patients the spiritual, emotional, and financial help in order to facilitate the final care at home.

Elisabeth Kübler-Ross, 1969

6.1 General considerations

This thesis aims to investigate the prevalence of analgesic drug prescription over time, and the efficacy of treating pain and burdensome symptoms in Norwegian nursing home patients. People with and without dementia were included and a broad approach of outcome measures was used. The comprehensive tasks made different statistical analyses necessary. My work demonstrates a complexity faced by municipal healthcare professionals every day. The following discussion aims to enhance the quality of the work through a more critical appraisal, and to influence the clinical practice positively and to provide some implications for future research. Interestingly, our publications received high acknowledgement by editorials (Breivik, 2014, Achterberg, 2016), engaged colleagues, and the media, which demonstrates that the field of elderly care and symptom management in nursing homes is of high relevance for researchers, clinicians, and society.

6.2 Methods

6.2.1 Paper 1: A Cluster Randomized Controlled Trial (cRCT)

To investigate the efficacy of a pain management intervention, we chose to use cRCT as this has been described as a Gold Standard for this type of research (Stolberg et al., 2004). The statistical structures of cRCTs were introduced in healthcare research groups for the first time by Cornfield (1978), who also demonstrates that the procedure is less efficient compared with randomisation of single individuals to the control and intervention group (Cornfield, 1978). The reduced efficacy is caused by the fact that patients, responders, or proxy-raters are related to one cluster, group, or unit and thus might answer more similarly than individuals who give individual responses (Donner and Klar, 2004). In our study, precautions were taken to blind research assistants and caregivers to group allocation. However, despite these efforts cRCTs will always be difficult to blind completely because of the requirements in a nursing home setting and the risk of contamination (Husebo et al., 2011). To meet this disadvantage of reduced efficacy, the number of participants has to be increased and the intra cluster correlation coefficient is an important element in the statistical analyses. To meet these challenges, we adopted the sample size number as described in an earlier publication (Husebo et al., 2011).

A further criticism of cRCTs in general is that they are often produced under controlled conditions with a selected group of people, and thus exclude older adults and people with dementia (Rothwell, 2005). Multi-morbidity and polypharmacy are well-known reasons for exclusion and lead to the underrepresentation of this group of patients in relation to the assessment and management of pain. However, untreated pain is an important challenge in dementia and is known to trigger neuropsychiatric symptoms such as agitation, depression, and sleep disturbances (Ahn and Horgas, 2013). This recent article is the first study to explore specifically the effect of pain management on the intensity of pain in nursing home patients with advanced dementia. Our study is produced under comparable conditions to the participants' daily lives as it is performed in the nursing home setting. These circumstances were also highlighted by Breivik (2014), who emphasised in his editorial that this

publication changed the current evidence from lowest (authors' opinions) to highest (cRCT) level (Breivik, 2014).

The internal validity of a study reflects the causal relationship between the variables studied. Hence, strong internal validity is the absence of systematic or random error/bias. A systematic error can be a recall bias, selection bias, allocation bias, background variables/confounders, misclassification/-stratification, and performance or detection error and error due to dropouts. The results might happen by chance, due to a random error, or in the form of a causal relationship (Akobeng, 2008).

In Paper 1, the internal validity is suggested to be strong especially regarding the random errors. Baseline data are equally distributed among the two groups and reduce the likelihood for allocation bias. The large number of patients with pain intensity scores at baseline included (n=327) is sufficient to detect change with significant levels of P<0.001 and thereby rule out type 1 errors (reject true hypothesis), and large enough to rule out type 2 errors (fail to reject false hypothesis) as the power was calculated and the needed number was exceeded. We suggested a Hawthorne effect, also referred to as a motivation bias, which might relate to staff learning or anticipation of effect. This effect did not last over time and the intervention group conferred benefits from the intervention at all time points compared with the control group. Our robust randomisation, large number of patients and clusters, and statistical testing using nursing home and cluster as nestling levels in multilevel mixed models, should be sufficient contextual factors to avoid systematic bias. The trial was not blinded with a placebo but both the individual and the caregiver rating were blinded to avoid performance bias. The results were not affected by a systematic difference due to drop-out rates as they were equally distributed between the control and intervention groups during the eight weeks of intervention.

Since we used secondary analyses of a cRCT that investigated the efficacy of treating pain on agitation, the prevalence of pain was not one of the inclusion criteria. Future studies should include patients with dementia and clinical relevant pain at baseline. In Figure 4, we show a mixed effect multi-level modelling that includes 203 patients

with pain intensity scores ≥3 at baseline. There were no differences in pain intensity scores between the control (mean 5.3 SE 0.2, n=99) and intervention (mean 5.4 SE 0.2, n=104) group, at baseline (P=0.642). Excluding persons without pain, the baseline pain intensities were higher compared with the original findings. The intervention group showed a significant change from baseline, but only slightly larger compared with the original findings in Paper 1 (ATE -1·74, SE 0.30, P<0.001). The change was in large parts due to the change in the control group.
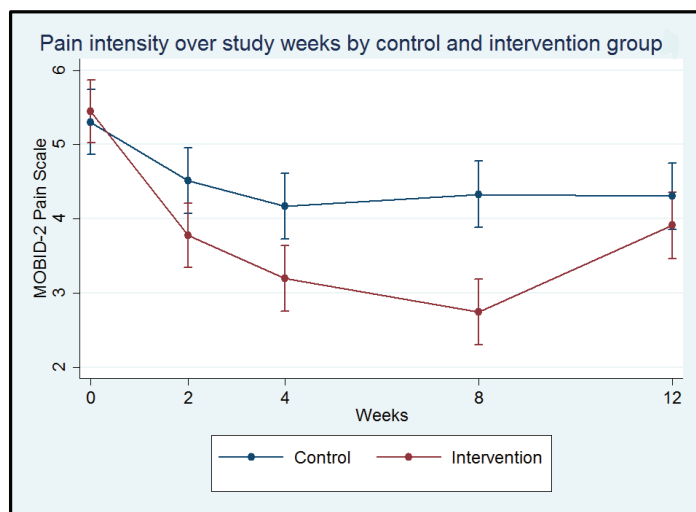
Figure 4: Pain intensity scores assessed by MOBID-2 Pain Scale in the control and intervention groups during eight weeks of treatment and a four-week wash-out period. Only people with baseline scores ≥3 were included.

6.2.2 Paper 2: An Epidemiological Study

We performed an observational trend study including four study samples to investigate analgesic drug prescriptions in Norwegian nursing homes, from 2000 to 2011. The analgesic drug prescriptions trend towards an increase, as from 2000 to 2011 we found a 65% increased prescription. Another important finding was that the analgesic drug prescription was related to having dementia until 2009, but in 2011 we found an equal prescription and no relation to dementia in 2011. Age and gender affected individually the prescribing patterns: women and the oldest old received most analgesics. This suggests that age and gender must be adjusted for in future

studies estimating probabilities in analgesic prescription and also as confounding factors.

Our study is limited by the fact that with the exception of the 99 patients examined in both 2004 and 2011, none of the included 5,798 patients were evaluated more than once. This means that we are not able to report trend analyses within the single cohorts but can only demonstrate the trend of analgesic use over one decade, in general. In addition, we did not register the doses, duration, and use of 'as needed' medication. Another weakness is the lack of valid pain intensity scores assessed by a validated pain tool, before and after pain treatment was started. Thus, we are not able to answer the question of whether the treatment was administrated effectively and the right patient received the right medication and at the right time. In the nursing home setting, inappropriate prescribing patterns and medication errors have been prevalent (Haasum et al., 2012).

The four study samples we have contain medication records from studies that were already collected. This means that each study was already performed and varied in criteria for eligibility, education of assessors, and the study aim. This might have introduced bias to the study selection because there were different nursing homes that were selected for different reasons for the different study samples. We could have investigated the same patients over time prospectively, but in addition to being a costly method it does not answer how analgesic drug use has developed until now. We could have included only the sample of 2004 and 2011 since they used the same nursing homes with the same criteria for inclusion/exclusion and the same research question and variables. However, by including the 2000 sample we were able to answer how the prescription of analgesic drugs changed over a whole decade. Regional variations in analgesic prescription may have influenced our results. However, as we use methods comparable with those adopted in other studies, and also find a comparable result, we suggest that the impact of local variations on the analgesic prescription is low (Pitkala et al., 2015).

All epidemiological studies introduce the question of covariates and variable selection. The selection of what variables to include is important either to rule them out as confounding factors, or background factors (Fletcher et al., 2012).

We used the nursing home as nestling level, suggesting a control for preferences by the prescribing doctors and educational packages of pain treatment provided. We also adjusted all analyses for listed variables, such as age, gender, and type of nursing home unit. There still might be confounding variables that we were not able to collect, especially clinical variables of pain intensity, delirium, and side effects of analgesic drug use. Further, the introduction of guidelines or educational packages may be relevant variables affecting the analgesic prescribing pattern in Norwegian nursing homes.

6.2.3 Paper 3: A Prospective Trajectory Study

A prospective trajectory design following a cohort with individual assessments from admission to a nursing home and for three years or until death is robust enough to rule out recall and selection bias. Patients living in a nursing home for many years are potentially a different population compared with the newly admitted people included in our study. All participants met the same inclusion and exclusion criteria and were assessed by the same variables and tests. Compared with Paper 2, these data are not constrained by existing data sets.

There are some limitations to the rigour of the prospective design, as well. Data are produced under the conditions of staff learning and motivation, and thereby symptom reporting can be influenced by learning and result in over reporting of clinical symptoms such as pain and anxiety. More importantly, it is not clear how the prospective follow-up of patients and caregivers acts as an intervention. Staff might score a symptom and thereby give a medication, or justify medication provided due to the symptoms scored.

We imposed a cut-off of one year on time from admission to death. The advantage of a one-year cut-off is to identify clinical symptoms related to a trajectory into the last days and hours of life. This might introduce a misclassification bias for some subjects

dying shortly after where the cut-off is placed and will be so wherever this cut-off is placed. We suggest that one year is valid because only two patients died the first month after admission, and we are now able to distinguish clearly between groups.

Medication data administered on the day of imminent dying and the day of death were collected prospectively and directly by telephone interview between the responsible nurse and the research assistant. Whilst this was a time-consuming procedure, we still suggest that it is the most effective and correct registration of ongoing treatment, which also included the "as needed" medication.

Previous longitudinal studies have used fixed assessments over a time period in nursing home patients with dementia (Mitchell et al., 2009), retrospective assessments of the last year with last assessment three months before death (Estabrooks et al., 2015), or prospective follow-up of patients over time where the last assessment before death was provided retrospectively (Brandt et al., 2006a, Hendriks et al., 2014, Klapwijk et al., 2014, Hendriks et al., 2015).

6.2.4 Assessment scales - validated in people with dementia

Our main outcome measure in Papers 1 and 3 is the MOBID-2 Pain Scale. Initially, the MOBID Pain Scale was developed and validated with seven items (observation at rest, moving hands, arms, and legs, turning in bed, sitting on the bedside, and mouth care) in people with advanced dementia (Husebo et al., 2007). Internal consistency showed very good kappa agreement between raters, which increased to over 0.90 after exclusion of the two items for observation and mouth care. Inter-rater reliability was also proven as good to very good. The further development of the MOBID Pain Scale to the MOBID-2 Pain Scale included assessment of pain that might be related to the musculoskeletal system (MOBID-2 part 1) and to the internal organs, head, and skin (MOBID-2 part 2) (Husebo et al., 2010). The MOBID-2 shows good to excellent validity and reliability (Husebo et al., 2010). Most relevant for our studies is the fact that the MOBID-2 Pain Scale has proven to be responsive to change after initiation of pain management, and thus is capable of assessing the effect of treatment during analgesic interventions of a cRCT (Husebo et al., 2014b).

Other screening or outcome scales used in our papers are the MMSE, CDR, FAST, Barthel ADL Index, and PSMS. For screening purposes we used the MMSE scale that was developed and validated in people with dementia, and has a Norwegian version and comes with a variety of different settings (Folstein et al., 1975, Braekhus et al., 1992). The MMSE has shown a floor effect, which might lead to an increasing number of people classified with advanced dementia. In Paper 1, we used the MMSE to identify patients able to consent (Etchells et al., 1999). We assessed the level of dementia by CDR or FAST in all three papers: FAST was used in Paper 1, CDR in Paper 3, and both tools in Paper 2. The FAST is not validated in Norwegian but is used routinely for clinical and research purposes in the nursing home setting (Testad et al., 2010). The CDR is validated and widely used (Nygaard and Ruths, 2003, Selbaek et al., 2007).

In Paper 2, we included four different samples where three assessed cognitive function using CDR, and only the 2009 sample used the FAST. This might have introduced a different classification of patients, either that patients classified with dementia with CDR were not classified with dementia by FAST, or vice versa.

The Barthel ADL Index has good validation in aged adults but not those with multiple diagnoses, needs, or dementia. It is also found to have a floor and ceiling effect. This is less of a concern in our population of frail persons with dementia, compared with the concern of not having an interval scale, overall Likert scale, or a clear interpretability scoring system (Sainsbury et al., 2005).

6.2.5 Assessment scales - not validated in people with dementia

In Paper 3, we included the ESAS, KPS, and the RAI-PC scales. These tools are used in people with dementia in general, although they are not validated for use in dying people with dementia. This means that the sensitivity and specificity in dying individuals with dementia is unknown, as is the validity and reliability in this setting. Despite these drawbacks, we selected these tools because they include a wide range of burdensome symptoms which might be present at the end of life.

To evaluate change in intensity scores over time and during treatment, it was further important to include scales with continued intensity measures because dichotomous registrations are not able to detect symptom intensity change.

Although not investigated for validity and reliability in dying patients with dementia, the RAI-PC has been used in this population by others (Brandt et al., 2006a). The ESAS is used in people with dementia and validated for proxy-rating (Nekolaichuk et al., 1999a, Nekolaichuk et al., 1999b, Pautex et al., 2003, Yang et al., 2016).

6.3 Discussion of the results

6.3.1 Pain and pain management associated with age, gender, and dementia

Our three publications contribute novel and unique results that strengthen this thesis. In the following, I aim to discuss our approach as a whole, including different aspects such as age, gender, and dementia, and also pain and pain management across the studies.

Age Patients in our studies show a mean and median increase in age of two years from 2000 (median 85, range 65-101) and to the REDIC study (2012-2014) (median 87, range 65-106), confirming the nursing home setting as increasingly a service for the oldest old (Table 8). It also reflects our society's ageing population. The increasing age over years has been observed by comparable studies in the nursing home setting (Ruths et al., 2013). People with dementia have a higher age compared with those without dementia, in memory clinics, home care service, and in the nursing home (Vossius et al., 2015). Thus, increasing age may follow the rising proportion of persons with dementia in the latter context.

Gender Demonstrated in Table 8, the proportion of women is smaller at admission to a nursing home compared with the stable proportions seen over time in the samples of Papers 1 and 2. This suggests a higher survival rate in women after nursing home admission. Female gender and increased age were also associated with increased analgesic drug prescription (Paper 2). Baseline data by the REDIC study also confirmed a crude odds ratio association between analgesics and female gender (P=.040) but not between analgesics and age (P=.074).

Dementia The proportion of people with dementia has risen over the years from 76% in 2000 to 87% in 2012/2014, a development also reported by (Helvik et al., 2015). This proportion is higher compared with home-dwelling people with dementia (42%) (Wergeland et al., 2014).

Pain According to Table 8, we find that the prevalence of moderate to severe pain (MOBID-2 Pain Scale ≥3) seems to be lowest at admission (37%), and that it shows

an increasing trend towards the day of imminent dying (65%) (Paper 3). This prevalence widely corresponds with results in Paper 1 (62%). In Paper 3, we also demonstrated that 46% of the patients (95% CI; 41-51) have moderate pain and 16% (95% CI; 13-21) have severe pain. The findings imply daily suffering for the general nursing home population.

Comparable prevalence results are reported from Finland (57%), the Netherlands (43%), and Italy (32%) (Achterberg et al., 2010). Using the MDS as an outcome measure, the study found moderate to severe pain intensity in over 50% of cases in all of these countries. The proportions of moderate to severe pain found in our study are higher compared with outpatients with cancer diagnoses (23%) (Oosterling et al., 2016) but comparable with patients hospitalised in the palliative care setting (83%) (Harada et al., 2016).

In Table 8 we show that in addition to the already mentioned results regarding age, gender, dementia, and pain intensity, the physical function and most painful locations shift over time from admission to death. Patients have less dependence upon admission compared with the average nursing home population found in Paper 1 and previous findings (Mjorud et al., 2014). Between admission and day of imminent death, the KPS unsurprisingly shows a change in mean from in need of medical assistance to very ill.

The three most painful locations at admission correspond to the ones found in the average nursing home population (Paper 1): moving the legs, pelvis, and turning in bed. On the day of imminent death, care-staff report that moving the patients induces the most pain when turning, sitting up in bed, and moving the legs. On the day of death, sitting up in bed might be avoided, but turning in bed is considered to hurt the most, followed by pain from the pelvis and moving the legs.

Table 8: Demographic details, physical function, overall pain intensity and prevalence in study samples included in Papers 1 and 3

| Characteristics	Paper 1 Pain-BPSD	Paper 2 2000	Paper 3 2011	Baseline REDIC	Imminent dying	Day of death
Age, mean (SD)	85 (7)	84 (7)	86 (8)	86 (8)		
Gender, female %	74	70	71	64		
Dementia, %	87	76	83	87		
ADL function, Barthel mean (SD)[§]	8 (6)					
ADL function PSMS mean (SD)[#]				15 (5)		
Karnofsky (100-0)[†]				54 (30)	16 (10)	
MOBID-2 Smerteskala						
Hands, mean (SD)	0.9 (2.9)			0.4 (1.4)	1.3 (2.6)	0.6 (1.5)
Arms, mean (SD)	1.7 (2.4)			1.0 (2.0)	1.9 (2.5)	1.0 (1.8)
Legs, mean (SD)	2.3 (2.8)			1.3 (2.2)	2.9 (3.1)	1.4 (2.5)
Turn, mean (SD)	2.0 (2.7)			1.2 (2.1)	3.6 (3.2)	2.6 (3.2)
Sit, mean (SD)	1.8 (2.6)			1.1 (1.9)	3.0 (3.2)	0.9 (2.3)
Head, mouth neck, mean (SD)	1.2 (2.1)			0.6 (1.5)	2.0 (3.0)	0.9 (2.0)
Heart, lung, chest, mean (SD)	0.8 (1.7)			0.4 (1.2)	1.1 (2.2)	0.9 (2.0)
Abdomen, mean (SD)	0.9 (1.8)			0.7 (1.6)	1.1 (2.1)	1.0 (1.9)
Pelvis, genital organs, mean (SD)	1.7 (2.6)			1.3 (2.3)	2.3 (2.7)	1.5 (2.3)
Skin, mean (SD)	1.6 (2.4)			0.7 (1.7)	2.0 (3.0)	1.0 (2.2)
Total score, mean (SD)	3.7 (2.6)			2.1 (2.1)	4.0 (3.0)	2.7 (2.8)
Proportion pain 0-2, %	38			63	35	55
Proportion pain 3-6, %	46			33	53	41
Proportion pain 7-10, %	16			4	12	4

[§]ADL scale (0-20): higher score equals better function
[#]ADL scale (6-30): higher score equals more dependence
[†]Higher score equals better function

Pain management The analgesic drug prescription increases substantially (65%) over time in Norwegian nursing homes (Paper 2) and prescribing patterns seem to be associated with the presence of pain (P<.001) (Paper 3). However, this does not guarantee that the pain management is adapted individually to the patient's pain level. Analgesic drug use in nursing homes does not correspond to the stable consumption in the general population and in home-dwelling people aged 75 years old and older (Fig. 5). However, it is encouraging to find an equal prescription independent from the level of dementia that is not in line with other recent findings (Tan et al., 2015). We also find a continuous growth in analgesic drug prescriptions in persons with dementia, and not in persons without dementia. Thus, increased monitoring of

treatment with association to age, gender, and level of dementia is needed. Further, the results of our studies underline the need for recommendations and educational packages for nursing home patients and people with dementia.
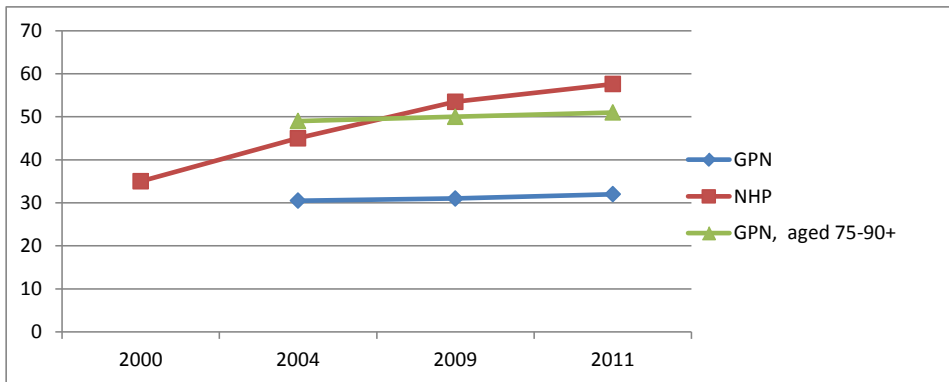
Figure 5. Total amount of prescribed analgesics (N02+M01) based on data from Paper 2 and the NorPD.
GPN=General population of Norway
NHP=Nursing home population, Paper 2

Comparable trends are reported from the United Kingdom and Denmark (Zin et al., 2014, Jensen-Dahm et al., 2014). In Denmark a worrying upswing in opioid use finds that up to 38% of people with dementia are treated with opioids, and 28% with strong opioids in Danish nursing homes (Jensen-Dahm et al., 2014). Prescribing patterns are mainly based on long acting transdermal applications of buprenorphine and fentanyl patches. There are only very few studies investigating the effects and side-effects of opioid use in elderly people with dementia (Habiger et al., 2016), and our own experiences recommend a more than careful use because of severe side-effects such as drowsiness, impaired cognition, loss of appetite, and increased balance disturbances.

6.3.2 Pain treatment effect – does it help, clinically?

Paper 1 reports one of the first studies to investigate the effect of pain management on pain intensity in people with dementia. These secondary analyses of a larger cRCT are based on two "assumptions": a SPTP and the efficacy assessment outcome measure MOBID-2 Pain Scale. Until now, clinical studies have been hampered by the lack of standardised treatment approaches and responsive tools able to assess change

after the treatment has been initiated. Thus, the results of our study may also be questionable.

We developed the SPTP based on clinical guidelines for older adults that have been published by the American Geriatrics Society in 1998 with repeated revisions in 2002 and 2009 (AGS-Panel, 1998, AGS-Panel, 2002, AGS-Panel, 2009). Although these guidelines are not specifically formulated for people with dementia, they highlight careful titration of the drugs and combination of two or more drugs with complementary mechanisms to improve pain relief with less hepatic and kidney toxicity and side effects. Following these recommendations, we also used the antiepileptic pregabalin in people suggested to be in neuropathic pain caused by, for instance, stroke or diabetes. Although we only included 12 participants, our data indicate a significant benefit especially important in light of the large group of people with dementia suggested to suffer from neuropathic pain associated with white matter lesions after stroke (Scherder et al., 2003a). To our knowledge, this is the first pain study including an antiepileptic drug as pain treatment in people with dementia.

The largest group of participants in the intervention group of Paper 1 was treated with paracetamol. Such treatment is well tolerated and only 2 of the 120 patients left the study following their families' wishes. Paracetamol seems to be effective and well tolerated, and can thus be recommended as a first-line medication to treat pain in people with dementia. Although we did not find an overall effect of pain treatment on ADL function, the isolated group of "paracetamol receivers" demonstrated a significant improvement in their activities (P=0.04). These results support earlier suggestions that individual pain treatment with paracetamol may improve physical function and activities in daily living (Chibnall et al., 2005).

Interestingly, participants in the intervention group demonstrated a significant worsening of pain intensity when analgesics were discontinued in the wash-out period. Contextual evidence has also been suggested by other analyses of this cRCT demonstrating the efficacy of treating pain on behavioural disturbances such as agitation, depression, apathy, and sleep and eating disturbances in people with dementia (Husebo et al., 2011, Husebo et al., 2014a). To conclude, findings

evidentially indicate the importance of immediate and individual pain management in people with dementia based on clinical appropriateness.

The other important "assumption" in Paper 1 has been the use of the primary outcome measure MOBID-2 Pain Scale. The latest version of the AGS Panel on Persistent Pain in Older Persons guidelines (2009) recommends the use of a validated pain assessment instrument (AGS-Panel, 2009). However, recommendations do not discuss the importance of the measurement property: responsiveness. In people with dementia, self-reported pain and change in pain intensity is invalid. Thus, the pain state has to be evaluated by a proxy-rater who uses a validated observational pain tool. To improve the treatment, this tool has to be practical and responsive. In light of this, the MOBID-2 Pain Scale is currently the only tool tested for reliability, validity, and responsiveness to change. This is of key importance and makes the MOBID-2 Pain Scale a recommendable tool to assess the efficacy of pain treatment interventions in RCT studies.

6.3.2 Different end-of-life trajectories

In Paper 3, we find that 25% of the patients admitted to a nursing home died within one year of admission. Pneumonia, heart failure, and dementia were the main underlying causes of death, and these results are supported by others who found that survival is reduced in persons with dementia by pneumonia, febrile episodes, and eating problems (Mitchell et al., 2009).

Previous studies have discussed the differences in the end-of-life trajectories in patients with cancer diagnoses, heart and lung diseases, and long-term illnesses (Harris, 2007, Murray et al., 2005). The fluctuating course of dementia may be prolonged over many years and characterised by multiple diseases or co-morbidities (Murtagh et al., 2004). This is in contrast to cancer, which follows a slower decline initially, but then shows a rapid decline near the end. This imposes a better planning for the last stage of life, as early and accurate identification along with the trajectory are more predictable (Murray et al., 2005).

6.3.4 How to predict the day of imminent dying?

In our study (Paper 3), almost 40% of the patients were not identified in advance as dying by their primary caregiver. This has important consequences because people not recognised to be dying do not receive the necessary attention, communication, and treatment. On the other hand, those identified as imminently dying (61%) had significant fatigue and poor appetite. These symptoms were also highlighted by a Dutch nursing home study including 516 patients at the end of life (Brandt et al., 2005a). The responsible physicians found little fluid (43%) and nutrition intake (25%), fatigue (32%), and dyspnoea (18%) to be indicators for reduced survival (less than six weeks) (Brandt et al., 2005a). This study also demonstrated that 93% of patients could be identified when they had less than one week to live (Brandt et al., 2006b). Important differences in relation to our results may be caused by the challenge to make a reflected team-decision about the day of imminent dying and then to call the research nurse on that day.

Symptoms of pain, dyspnoea, or agitation were not associated with the day of imminent dying in our study. This is interesting because symptoms of fatigue and reduced appetite alone do not explain the start of medical treatment with morphine, benzodiazepine, or anticholinergics. Pneumonia and heart failure at the end of life may lead to dyspnoea and pain. However, we are worried about the fact that staff may not be able to recognise and interpret related life-limiting symptoms.

6.3.5 Symptom severity at the day of imminent dying

As stated, we use proxy-rated tools which might influence the symptom proportion and severity (Harris, 2007). This strengthens the requirement of the tools that must contain relevant symptoms for the patient group and validated for proxy-rating. Increased responsibility of care should also be emphasised in staff training on symptom assessment and knowledge of the tools. To exemplify, when we investigate pain and dyspnoea at admission in all the 691 persons included, we find 45% of the patients to have pain and 22% to have dyspnoea, which is lower than comparable investigations (Hendriks et al., 2015). Hendriks and colleagues (2015) assessed all symptoms on a dichotomous scale of present or not, and find the proportional

prevalence of agitation to be 57%, pain 52%, and dyspnoea 19% at admission. In our study we did not investigate agitation using the ESAS but with the neuropsychiatric inventory, and found that 11% had agitation, which is substantially lower compared with the almost 60% found by Hendriks and colleagues (Hendriks et al., 2015). Few studies offer the comprehensive list of symptoms that we provide with an intensity score. However, we find that our results are more in line with studies who do use the ESAS tool, although we use a severity of 3 and they use a cut-off at 6 (Brandt et al., 2006a).

Although national guidelines for dementia increasingly also focus on end-of-life care, there is a systematic lack of prognostication and concrete suggestions on how to provide comfort to dying elderly people (Nakanishi et al., 2015). In the following table 9 below, we mention some typical differences between end-of-life care for cancer patients compared with people with dementia.

Table 9. End-of-life care comparing persons dying from cancer and persons dying from dementia

Cancer	Dementia
Predictable trajectory, where prognostication and recognition of the last days are possible	Fluctuating trajectory, comorbidities, and recurrent episodes of decline in function followed by improvement
Clear when to plan and for what scenario	Planning must be made well in advance
Advance care planning can be provided because the trajectory is clear	Advance care planning is complicated
Clear care goals can be provided ahead	Care goals shift
Self-report is often possible	Proxy-rating is needed
Well validated assessment tools	Lack of validated tools assessing severity
Implementation of care and pharmacological treatment and effect is well documented, providing comfort prediction	Unclear pharmacological effect, very individualised, and with many comorbidities
Enhanced communication with patients and family	Person-centred care possible, although communication with person and care givers often complex
Well known what symptoms to assess	Symptoms less clear
Staff competence is adjusted to patient need	Staff competence often low
Palliative teams are cross-professional and easy to reach	Palliative competence is less implemented and problematic to reach
Nutritional efforts can be planned	Low effect and use of feeding tubes
Hospital admissions are planned	Hospital admissions are acute and unplanned
Stopping burdensome interventions and hospital admissions	Often many burdensome and unrequired interventions like transferals, oxygen, fluid, and feeding tubes
Spiritual and psychological support possible to assess efficiency	Spiritual and psychological support not often provided
Education programmes implemented	Few education programmes available

6.3.6 Symptom severity and management on the day of death

We find that the proportion of persons experiencing moderate and severe symptom intensity declines for most symptoms over time. However, this does not refute a high symptom burden on the day of death. In addition, respiratory symptoms like dyspnoea and death rattle increase. Considering the increase in symptom management, this is worrying.

The symptom severity we find regarding pain (46%) and agitation (3%) are lower compared with the findings of Hendriks et al. (2015), where physicians reflected back on the last week of life (Hendriks et al., 2015). The severity of dyspnoea that we find in our study (53%) is comparable with the 52% that Hendriks et al. (2015) found in their study. The severity of agitation (3%) and delirium (3%) that we find in our Paper 3 is substantially lower than previous studies (Hall et al., 2002, Hendriks et al., 2014, Hendriks et al., 2015). Hendriks and colleagues (2014, 2015) find that 35% of patients are agitated during the last week of life, and Hall and colleagues (2002) find that 30% experience delirium (Hall et al., 2002, Hendriks et al., 2014, Hendriks et al., 2015). It might be questioned if agitation and delirium are two distinct symptoms, or if both cover delirium. We added the symptom burden of the two and found that the symptom intensity lessened towards the day of death (28 to 19%, P<0.001). The identification of delirium is complex and in need of enhanced focus and improved tools. We did not include a specific instrument for delirium like the Confusion Assessment Method, which might have introduced an under-detection of delirium. Future research would benefit from designing and testing a tool to detect delirium in dying patients with dementia.

The suitability of assessment tools will affect the proportion of symptoms found, and this was the case for a small Dutch study investigating symptom severity and management in 24 nursing home patients with dementia during the last week of their life (Klapwijk et al., 2014). The MSSE was more sensitive and detected a higher proportion of pain (36%) compared with the EOLD-CAD tool (15%) (Klapwijk et al., 2014).

The provision of administered pharmacological treatment found by us is lower compared with previous findings of prescribed drugs during the last 24 hours of life (Jansen et al., 2014). This difference between prescribed and administered drugs might occur because the anticipatory drugs are not tailored to the person's symptoms and needs. However, there can also be a very rapid change in the individual needs of the patients for the physicians to change the treatment plan.

Opioids are also provided to nursing home patients to relieve dyspnoea (Hall et al., 2002, Hendriks et al., 2014, Hendriks et al., 2015). Therefore, it was unexpected that our Paper 3 did not find opioids associated with the amelioration of dyspnoea. There are several underlying causes for dyspnoea like congestive heart failure, fever, and lung oedema. Management will need to target the underlying cause of the symptom for better symptom relief. We found an effect of opioids on death rattle, which raises the question of whether the caregivers have misclassified these symptoms.

The most current evidence base is provided by the NICE guideline "Care of dying adults in the last days of life" in the United Kingdom. Pharmacological intervention studies comprised the management of pain, breathlessness, and noisy secretion. The evidence for pharmacological interventions was rated as either low or of very low quality in most of the studies, and most studies included only cancer patients (NCCMH, 2015). This review did not find any studies including persons with dementia solely. Thus, this leaves a considerable need for studies investigating the efficacy of drugs prescribed for symptoms anticipated at the end-of-life in people with dementia.

6.4 External validity

External validity or generalisability discusses the ability to refer the study results to other clinical circumstances, both national and international (Akobeng, 2008). We suggest that our results are representative for most of the Norwegian nursing home settings where about 50% of the patients have mixed dementia (Husebo et al., 2008). We expect that the stepwise protocol of treating pain, used in Paper 1, has the ability to impact prescribing routines and pain management in nursing home patients. Hopefully it also has a broad impact on patients and care givers, and will guide new research.

For Paper 2, the external validity is given in a national perspective by a broad inclusion of the high number of nursing homes. The follow-up of the same cohorts over time could be a future perspective. As we performed analyses on the 2004 and 2011 sample, to adjust for covariates, we have ensured representativeness to the general nursing home patient. Importantly, our study samples do not differ from other international nursing home samples, and thus the results can be applied to them. Small and large nursing homes in both cities and rural areas have been included, which enhances the generalisability to the general nursing home population.

Extrapolating results from Paper 3 to all dying Norwegian nursing home patients is more critical. Despite the inclusion of a high number of nursing homes (N=47) and number of participants (N=691), we only followed 134 patients to the day of death. Although this group of patients is larger than comparable samples, results cannot be generalised without further discussion. To our knowledge, this is the first study which follows dying people prospectively, as close as possible. Results have to be proven in national and international studies, followed by intervention studies to improve the situation for dying elderly people. Correct symptom assessment and management is important to ensure a dignified death. Our findings are of importance for future dying persons in nursing homes, their loved ones, and the staff caring for them.

6.5 Ethical considerations

All paragraphs of the declaration of Helsinki of June 1964 by the World Medical Association are vital for all research. For our studies there are some very important points to discuss: informed consent, ethic committees, vulnerable groups, and registration and dissemination of results (WMA, 2016). Four principles of medical ethics have been suggested by Beauchamp and Childress to unite deontological and teleological ethical theories (Beauchamp and Childress, 2001): autonomy vs. paternalism, beneficence, non-maleficence, and justice.

All studies included in this thesis have been approved by the regional ethical committees. Paper 1 also had approval from and was continuously controlled by the Norwegian Medicines Agency. The BPSD-pain and the REDIC study were registered at Clinical Trials.gov before the recruitment of study participants and had clear plans for dissemination of the results. Collecting data also obliges the researchers to use these data in accordance to *a priori* hypotheses. All researchers are obliged to use already collected data when possible, instead of performing new studies. These responsibilities have been well guarded by the included studies.

Including vulnerable individuals with the possibilities of experiencing additional suffering should be balanced with paragraph 13 of the declaration of Helsinki, stating that underrepresented groups should be provided access as participants in medical research. Of course, only as long as the possible harms are minimised and justified by therapeutic value to the persons participating. Excluding patients with dementia from medical studies might prevent them as a group from optimised treatment and best practice. According to the declaration of Helsinki, the use of placebo or no intervention is acceptable where no best practice exists. This is very relevant for our Paper 1 as we randomised individuals in clusters to intervention and used current practice as control. We did not remove any treatment. This means that the control group's daily care was expected to be the current best practice, also when we discontinued study drugs in the wash-out period. On the one hand, it can be argued that providing analgesic treatment for frail elderly adults might introduce harmful side-effects and cause maleficence, whereas on the other hand it can also be argued

that keeping persons from possible beneficial treatment over 12 weeks is both harmful and unjust.

In the Nuremberg code, of which the declaration of Helsinki originates, the first paragraph clearly states that participation in research is possible by voluntary informed consent (Nuremberg, 1949). In the current version of the declaration, seven paragraphs outline consent and in the 30th paragraph the declaration opens for involving persons incapable of giving informed consent by pursuing consent from the persons legally authorised as their representatives.

In Paper 2, study samples from 2000, 2004, and 2011 patients and the legally authorised representative for the person received information, and they were able to withdraw before or during the study. In the BPSD-pain and REDIC study the MMSE, was used as guidance (Etchells et al., 1999). The MMSE is merely a staging tool for cognitive capacity, but the most commonly used aid to evaluate ability to give informed consent. As suggested by the declaration of Helsinki, the ethic committees, and Norwegian legislation, consent can be obtained from authorised legal representatives (proxy-informed consent) when the individuals are unable to provide their own written consent. Our consideration was to use the outlined consent procedure: provide sufficient written and verbal information in a form understandable to the individual, provide sufficient time to understand the information, test to see if the information was understood, and ensure that the individual could reflect upon and judge the information (Warner and Nomani, 2008).

Longitudinal prospective studies provide the opportunity to approach patients to obtain consent at admission for observations also at the end of life. Such studies are very demanding and need substantial resources, however if not provided then such studies might be the reason why we lack clinical information and best practice today.

7. Conclusions

In this thesis, I highlighted various aspects of pain and symptom management in nursing home patients, from the efficacy of individual pain treatment, via prescription trends, to symptom severity and usefulness of pharmacological treatment in the last days and hours of life.

In Paper 1, our well-powered and robust study found that a SPTP significantly improved pain intensity in nursing home patients with moderate to severe dementia and behavioural symptoms. Pain treatment with paracetamol improved ADL. Our findings call for improved staff competence and pain assessment as a standardised approach for pain management.

In Paper 2, we found an overall increase in analgesic prescription in 65% of the participants from 2000-2011 in Norwegian nursing homes. The use of paracetamol and opioids increased by 113% and 118%, respectively. However, strong opioids showed the largest increase as they increased almost nine-fold from 2000 to 2011. In 2011, we did not find that the analgesic drug prescription differed between persons with and without dementia. Advanced age and female gender were associated with prescription of any analgesic agent.

Evolving from our Paper 3 is the identification of imminent dying by observing poor appetite and fatigue, which increased prediction accuracy to 61%. Further, we found that pain and burdensome symptoms ameliorated from the day patients were perceived to be dying until the day of death, except for respiratory symptoms that increased. Despite intensified pharmacological intervention, the symptom burden was still high on the day of death in nursing home patients.

7.1 Implications and future perspectives

This thesis arose from the Centre for Elderly and Nursing Home Medicine, Department of Global Public Health and Primary Care, University of Bergen, and has its strategic aims spread across the four pillars of implementation, research, education, and national and international collaboration.

Implementations that may arise from this thesis are systematic assessment of pain and burdensome symptoms from admission to a nursing home, over a nursing home stay, and to the last days and hours of life. Our SPTP, designed to lessen pain intensity in nursing home patients and to ameliorate burdensome symptoms at the end of life, can be implemented and follow the provided assessments. This thesis finds support for the use of pharmacological treatment in dying nursing home patients and urges their implementation in this setting. We were not able to relate our prescription data to patients' pain intensity and it is important to do so ahead, therefore a nursing home registry containing prescription data as well as clinical symptoms is needed.

Studies succeeding our investigations are continuing studies of the efficacy on different analgesic agents in placebo-controlled studies, including persons with dementia and pain. The interaction of pain intensity, analgesic agents, and physical function is barely investigated, but based on our findings it is of utmost importance to explore this in epidemiological studies, in trajectory studies following persons over time, and in RCTs. The impact of the discontinuation of analgesic agents on clinical outcomes like pain intensity, behaviour, and mood is beneficial for patients to explore in a RCT trial.

Our results show a substantially increased prescription trend of analgesic agents, and that for persons with dementia the trend continues. Our period of investigation was limited to one decade. In future studies, the analgesic prescribing patterns should be followed over a longer period of time to confirm the increase as a trend. Further, the prescribing patterns for patients must be investigated also in home-dwelling older adults with and without dementia.

This thesis calls for educational packages for nursing home and home-care service staff. Complex interventions and education are needed to be developed in robust research studies and implemented in nursing homes and home-care services. This responsibility must be taken seriously by all educators of healthcare staff, and thereby improve care for and shift focus onto people with dementia, who are the fastest growing group of persons in need of quality care.

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Appendices I-III

Appendix I

I

Table 4. Pharmacological recommendations in older adults according to relevant review articles and guidelines

Review/guideline	Analgesic	ATC-number	Indication	Dose and Range	Comments
Peripheral analgesics					
Abdulla et al. (2013) AGS-Panel (2009) AMDA (2012) APS (2005) Barber and Gibson (2009)	Paracetamol	N02BE01	-Mild to moderate pain -Nociceptive pain -Inflammatory pain -To enhance pain threshold in other pain states	-A daily dose of 1-4g/day FDA recommends 3g/24 hours	-Hepatic damage if max dose is exceeded -Concern about ongoing max dose, but increased liver transaminase not translated into liver failure -Rare skin reactions -Reduce dose by 50-75% in case of hepatic insufficiency, dehydration, poor or malnourished patients, high alcohol intake.
Abdulla et al. (2013) AGS-Panel (2009) AMDA (2012) APS (2005) Barber and Gibson (2009)	NSAIDs [†] and Cox 2 inhibitors	M01A-G M01AH	-Mild to moderate pain -Inflammatory and musculoskeletal pain	-Start with lowest dose of drugs with shortest half-life	-Ulcus bleeds, bronco spasms, renal deficiency affects potassium/sodium pump and may cause water retention followed by hypertension, oedema, and congestive cardiac failure. -Myocardial infarction. -APS finds corticosteroids safer in inflammatory pain -Short-term use only, and only one NSAID at a time
Weak Opioids					
Abdulla et al. (2013) AGS-Panel (2009) AMDA (2012) APS (2005) Barber and Gibson (2009) Huang and Mallet (2013)	Codeine	N02AA59	-Moderate pain -Nociceptive pain -Cough	-Trial use -Not given "as needed" in people with dementia -For infrequent pain -Prescribed with laxative	-Weak affinity for opioid receptors, unclear effect and titration in elderly -Effect inhibited by other medication, e.g. haloperidol and selective serotonin reuptake inhibitors (SSRIs) -Absent or altered effect might be due to lacking or duplicated polymorphic enzyme CYP2D6∞
Tramadol		N02AX02	-Moderate pain -Nociceptive pain -Neuropathic pain	-20% lower dose in aged individuals -Not to be administered concomitantly with SSRIs	May lower the threshold for seizures -May contribute to serotonergic syndrome in combination with SSRI or other serotonergic agents like tricyclic antidepressants and Venlafaxine -Not given "as needed" -Not possible to titrate due to SSRI component

Strong Opioids
Abdulla et al. (2013)
AGS-Panel (2009)
AMDA (2012)
APS (2005)
Barber and Gibson (2009)
Huang and Mallet (2013)

Drug	ATC code	Indication	Dosing	Notes
Morphine	N02AA01	-Moderate to severe pain -Nociceptive pain, -Neuropathic pain	- Should be initiated in a low dose, with slow titration -Usually 10-40 mg/day orally -Start with 30-50 % of doses -Prescribed with laxative	-Sedation, dizziness, nausea, vomiting, respiratory depression, constipation -Individual dosing -Can be combined with gabapentin in case of post-herpetic neuralgia or diabetes poly-neuropathy -Reduced renal excretion -Morphine metabolites may persist beyond pain relief -May accumulate by kidney insufficiency
Oxycodone	N02AA05	Neuropathic pain, inflammatory pain, neuropathic pain	- Should be initiated in a low dose, with slow titration Start with 10 mg -Start with 30-50 % of doses for other adults -Prescribed with laxative	-Side effect profile comparable with morphine
Fentanyl	N02AB03	Moderate to severe nociceptive or neuropathic pain	-12–25 mcg/h -Not in opioid naïve patients -Prescribed with laxative	-Side effect profile comparable with morphine: constipation, nausea, and drowsiness -No active metabolites -Transdermal administration has uncertainty in peak-time -Needs careful monitoring in older adults -Rashes to the skin -Preferred in hepatic failure
Buprenorphine	N02AE01	Moderate, severe Nociceptive, neuropathic	5 mcg/h patch -Prescribed with laxative	-Dizziness, nausea, constipation -Heat increases release, do not use heating pad

Hydromorphone Pethidine Methadone				-No evidence in aged individuals -Not recommended in aged individuals -Long half-life, multiple mechanisms or action, not in aged people and restricted to persons experienced with the drug
Adjuvant Therapy Abdulla et al. (2013) AGS-Panel (2009) AMDA (2012) APS (2005) Barber and Gibson (2009) McGeeney (2009) Haslam and Nurmikko (2008)	Amitriptyline Gabapentin Pregabalin	N06AA 09 N03AX 12 N03AX 16	Neuropathic pain	-Amitriptyline need 50% dose reduction, -Bioavailability is dose dependant in gabapentin, but pregabalin has a linear profile	-Arrhythmias, postural hypotension, sedation, delirium, glaucoma, urinary retention seen in amitriptyline use - Sedation, ataxia and oedema -Dose adjustment with renal failure, and malnutrition

ATC Classification System =Anatomical Therapeutic Chemical Classification System †NSAIDs=Non Steroidal Anti-Inflammatory Drugs ∝CYP=Cytochrome

Appendix II

II

Table 5. Symptom assessment instruments relevant at the end of life in persons with dementia

Authors	Tool	Content of the tool and scoring system	Psychometric property testing	Dementia
Rogers et al. (1998) Ewing et al. (2004) Ewing et al. (2006)	CAMPAS-R	Self-report of eight symptoms (pain, nausea, vomiting, constipation, fatigue, breathlessness, anxiety, and depression) rated on a Visual Analogue Scale for intensity and inference of symptoms.	Created and investigated for validity, showing good internal consistency and excellent criterion validity, and fair to good reliability	No
Portenoy et al. (1994)	CMSAS	Scoring of energy and appetite, pain, dry mouth, weight loss, drowsiness, shortness of breath, constipation, sleep, concentration, and nausea on a frequency scale from 0-4.	Created and investigated moderate to excellent validity and reliability	No
Volicer et al. (2001)	EOLD-CAD	Symptoms present in the last seven days of life (discomfort, pain, restlessness, shortness of breath, choking, gurgling, difficulty in swallowing, fear, anxiety, crying, moaning, serenity, peace, and calm) rated on a three-point Likert scale (range 14-42).	Developed and tested for moderate to good validity and excellent reliability	Yes
Volicer et al. (2001)	EOLD-SM	Self-report symptoms on a six-point Likert scale for severity in the last 90 days of life (pain, shortness of breath, depression, fear, anxiety, agitation, calmness, skin breakdown, and care resistance), ranging 0-45.	Developed and tested for good internal consistency and good reliability	Yes
Bruera et al. (1991) Nekolaichuk et al. (2008)	ESAS	Nine items (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath) each rated on a Likert scale (range 0-10).	Developed and tested for palliative care patients, with good to excellent validity and reliability	No
Armstrong et al. (2005)	MDASI	Scoring severity on a symptom scale from 0-10 on the following symptoms; pain, fatigue, nausea, sleep, upset, memory, drowsiness, lack of appetite, dry mouth, depression, vomiting, numbness, activity, mood, work, relations to others, and walking.	Initial validation for validity and reliability	No
Aminoff (2004)	MSSE	Ten items (agitated, screaming, pain, decubitus ulcers, malnutrition, eating disorders, invasive action, unstable medical condition, suffering according to medical or family opinion) rated yes or no for present or not present, and sub-divided into low-level suffering (0.3), intermediate suffering (4-6), and high-level suffering (7-10).	Created and used with patients with severe dementia, tested for moderate to good validity and reliability	Yes
Steel et al. (2003)	RAI-PC	Fifteen domains (demographics, admission data, physical condition including pain, dyspnoea, falls, intake and nutrition, condition of the skin, cognition, communication, mood and behaviour, psychosocial function, ADL, continence, medical treatment, other treatment, decision making, social support, referral information) rated present or not present.	Investigated for good to excellent validity and moderate to excellent reliability	Yes

Appendix III

III

Table 6. Assessment instruments used in any of the papers arising from this thesis

Author	Instrument	Content of the instrument	Tool characteristics and psychometric properties	Paper
Hughes et al. (1982)	CDR	Cognitive staging tool	The CDR consists of five steps (0-3) distributed as follows: no dementia (0 and 0.5), mild dementia (1), moderate dementia (2), and severe dementia (3). CDR is a reliable, valid, and feasible tool, validated in the Norwegian language.	2&3
Reisberg (1988)	FAST	Cognitive staging tool, assessing dementia in seven steps from no dementia to severe dementia.	The FAST stages dementia from normal cognition (stage 1) to most severe dementia (stage 7): no dementia (1-2), mild dementia (3), moderate dementia (4-5), and severe dementia (6-7).	1&2
Folstein et al. (1975)	MMSE	Cognitive staging tool with eight domains (orientation to time and place, short-term recall, attention, and calculation, long-term recall, language, repetition, complex commands)	The MMSE is a 30-point questionnaire (0-30); severe impairment (0 -11), moderate impairment (12-17), mild impairment (18-23), and no impairment (24-30). The MMSE is widely used and demonstrates good validity and reliability.	1&3
Mahoney and Barthel (1965)	Barthel ADL Index	Personal ADL are assessed by 10 domains (bowel, bladder, grooming, feeding, bathing, transfer, stairs, toileting, mobility, dressing).	The Barthel ADL index ranges from 0-20, with a lower score indicating higher dependence in ADL functions on ten items.	1
Vincent (1984)	KPS	Physical function	The KPS scale is an 11-step rating scale from normal function (100) to dead (0). KPS demonstrates good psychometric properties in cancer patients and in elderly people.	3
Lawton and Brody (1969)	PSMS	Personal ADL are assessed by six domains (toileting, eating, dressing, grooming, transfer, and bathing)	The PSMS has six domains, each scored on a scale from 1-5 (range 6-30). Increasing numbers means increasing dependence in daily functioning. It has good reliability and validity, and is sensitive to change in severe dementia.	3
Bruera et al. (1991)	ESAS	Distressing symptoms related to the end of life (pain, fatigue, drowsiness, nausea, appetite disturbances, dyspnoea, depression, anxiety, wellbeing, sleep, vomiting, delirium, agitation, death rattle, and constipation)	The ESAS evaluates sub-item intensity on an 11-point Likert scale (range 0-10). Intensity is grouped as none to mild (0-2), mild to moderate (3-6), and moderate to severe (7-10). The ESAS has shown good psychometric properties, and has been used in dying people with dementia.	3
Husebo et al. (2010)	MOBID-2 Pain Scale	Pain intensity and pain location from musculoskeletal pain (Part 1), and pain from the internal organs, head, and skin (Part 2)	The MOBID-2 Pain Scale assesses pain intensity and pain location based on a patient's pain behaviour during standardised and guided movements. The 10 items are scored on a 0-10 numerical rating scale (0=no pain, 10=severe pain). Based on all observations, the patient's overall pain intensity is rated again on a 0-10 scale. MOBID-2 Pain Scale has excellent reliability, validity, and good	1&3

responsiveness.

| Steel et al. (2003) | RAI-PC | Distressing symptoms, care, and treatment provided. | The RAI-PC consists of eight domains (symptoms, communication, mood, functional status, preferences, social relations, spirituality, and treatments), although we added items for mouth care, bedsores, and nutrition. | 3 |

Papers I-III

Paper I

I

EJP

ORIGINAL ARTICLE

Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: A cluster randomized trial

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Conflicts of interest
C. Ballard declares associations with the following companies: Acadia, Bristol-Myers, Squibb, Esai, Janssen, Lundbeck, Novartis and Shire. D. Aarsland declares associations with the following companies: DiaGenic, GE Healthcare, GlaxoSmithKline, Lundbeck, Merck Serono and Novartis. A. Corbett declares associations with Novartis, Lundbeck, Bial and Acadia. Other authors have no disclosures to report.

Abstract

Background: Pain is frequent and distressing in people with dementia, but no randomized controlled trials have evaluated the effect of analgesic treatment on pain intensity as a key outcome.

Methods: Three hundred fifty-two people with dementia and significant agitation from 60 nursing home units were included in this study. These units, representing 18 nursing homes in western Norway, were randomized to a stepwise protocol of treating pain (SPTP) or usual care. The SPTP group received acetaminophen, morphine, buprenorphine transdermal patch and pregabalin for 8 weeks, with a 4-week washout period. Medications were governed by the SPTP and each participant's existing prescriptions. We obtained pain intensity scores from 327 patients (intervention $n = 164$, control $n = 163$) at five time points assessed by the primary outcome measure, Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale. The secondary outcome was activities of daily living (ADL). We used a linear intercept mixed model in a two-way repeated measures configuration to assess change over time and between groups.

Results: The SPTP conferred significant benefit in MOBID-2 scores compared with the control group [average treatment effect (ATE) -1.388; $p < 0.001$] at week 8, and MOBID-2 scores worsened during the washout period (ATE $= -0.701$; $p = 0.022$). Examining different analgesic treatments, benefit was conferred to patients receiving acetaminophen compared with the controls at week 2 (ATE $= -0.663$; $p = 0.010$), continuing to increase until week 8 (ATE $= -1.297$; $p < 0.001$). Although there were no overall improvements in ADL, an increase was seen in the group receiving acetaminophen (ATE $= +1.0$; $p = 0.022$).

Conclusion: Pain medication significantly improved pain in the intervention group, with indications that acetaminophen also improved ADL function.

What's already known about this topic?
- Many people with dementia experience pain regularly, but are not able to communicate this to their carers or physicians due to the limited self-report capacity inherent in the symptomatology of dementia.
- Few studies have investigated the direct effect of pain treatment on pain intensity in patients suffering from dementia, with previous studies using proxy measures of behavioural symptoms.

What does this study add?
- A stepwise protocol to treat pain in nursing home residents with moderate to severe dementia significantly reduced pain intensity.
- Pain treatment by acetaminophen improved activities of daily living.
- There is an urgent need for a standardized approach to assessment and treatment of pain for nursing home residents with dementia.

1. Introduction

Dementia affects approximately 10 million people in Europe, and this is expected to double every 20 years as the population ages (Kalaria et al., 2008). One-third of people with dementia reside in nursing homes (NHs). In addition to the distress experienced by these individuals as a result of their condition, many also experience pain (Achterberg et al., 2007). The precise prevalence of pain is unclear, but estimates indicate that up to 80% of NH patients are in acute or chronic pain (Husebo et al., 2008; Achterberg et al., 2010, 2013). The majority experience persistent pain lasting 6 months or longer (Pickering et al., 2006). The most common types of pain are musculoskeletal, such as arthritis, or neuropathic pain as result of diabetes or stroke (Scherder and Plooij, 2012). Despite the high prevalence of pain in these individuals, assessment is difficult due to the loss of cognitive and communicative abilities.

Pain is distressing for the individual who experiences it and often correlates with key symptoms, ranging from problems with coordination and memory to changes in personality and behaviour. This can also lead to an increased risk of falls (Deandrea et al., 2010; Huang et al., 2012), behavioural and psychological symptoms of dementia (BPSD) such as agitation and aggression (Hurley et al., 1992; Lin et al., 2011; Ahn and Horgas, 2013; Husebo et al., 2013), and depression (Cohen-Mansfield and Taylor, 1998).

In addition, undertreated pain affects social interaction, provokes sleep disturbances and reduces quality of life (Giron et al., 2002; Cipher and Clifford, 2004; Cordner et al., 2010). Furthermore, people experiencing BPSD due to pain may be inappropriately prescribed anti-psychotic medication, which can be harmful, rather than analgesia (Corbett et al., 2012a,b).

A limitation in the existing literature is the lack of large randomized controlled trial (RCT) studies with pain intensity as the main outcome (Corbett et al., 2012a,b). To date, no large-scale pain intervention studies have focused upon improvement of pain intensity as a key outcome (Lorenz et al., 2008). Most studies, including four RCTs, have utilized measures of BPSD, mood or activities of daily living (ADL) as proxy measures of pain (Manfredi et al., 2003; Buffum et al., 2004; Chibnall et al., 2005; Kovach et al., 2006). All RCTs were performed in the NH setting and with aged patients investigating the effect of pain medication on agitation. However, none of these trials included a measure of pain or a systematic pain management protocol.

The absence of data regarding the impact of pain intensity is, in part, due to the challenge of accurately identifying pain robustly. We recently developed and tested the Mobilization-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale for use in NH patients with dementia (Husebo et al., 2010). This article reports secondary analyses of an 8-week RCT with follow-up assessment after a 4-week washout period to investigate the effect of pain treatment on pain intensity in NH patients with dementia, assessed by the MOBID-2 Pain Scale.

2. Methods

The trial is registered at ClinicalTrials.gov (number NCT01021696) and at the Norwegian Medicines Agency (EudraCT nr: 2008-007490-20). Ethical approval was obtained in accordance with local law, by the Regional Committee for Medical Ethics, Western Norway (REK-Vest 248.08) and by the authorized Institutional Review Board of each participating institution.

2.1 Study design

This study was an 8-week RCT comparing the effect of the stepwise protocol of treating pain (SPTP) intervention with control in people with dementia living in Norwegian NHs. The trial included a 4-week washout period with additional follow-up at 12 weeks. The recruitment strategy of 18 NHs, patient samples and full study design has been described in our previous publication (Husebo et al., 2011).

2.2 Eligibility criteria

Participants included in this study were people aged 65 years and older residing in a NH for at least 4 weeks. Inclusion criteria were a diagnosis of Alzheimer's disease or other dementias according to Diagnostic and Statistical Manual of Mental Disorders, a Functional Assessment Staging score >4 (Reisberg et al., 1982) and clinically relevant behavioural disturbances defined as Cohen Mansfield Agitation Inventory score ≥39 (i.e., at least 1-week history of clinically significant agitation) (Cohen-Mansfield et al., 1989; Finkel et al., 1992). Only patients with moderate or severe dementia, defined as a score of <20 on the Mini-Mental State Examination scale (MMSE) (range 0–30), were included (Folstein et al., 1975). Residents were included independent of painful diagnoses, presumed pain or ongoing pain treatment. Residents were excluded if they had an expected survival of less than 6 months, severe psychosis or allergy to any of the study drugs. Written informed consent included a description of the study design, benefit and possible side effects of the trial. We took into consideration that even individuals with mild cognitive impairment might have impaired capacity to consent to research (Warner and Nomani, 2008; Ayalon, 2009) and obtained informed consent from all patients and all surrogates/caregivers or the authorized legal representatives. Caregivers also gave consent to participate as informants.

2.3 Intervention

The SPTP followed the latest recommendations of the American Geriatric Society (AGS) Panel for pharmacological management of persistent pain in older adults (AGS Panel on Persistent Pain in Older Persons, 2009) and is described in our previous publication (Husebo et al., 2011). All patients assigned to the treatment group were investigated individually by the responsible team, which consisted of the NH physician, the patient's primary caregiver, a pain therapist (B.S.H.) and a research assistant (R.K.S.). After a thorough discussion, the team agreed on the most appropriate pain medication and dosage according to the standardized SPTP protocol. Depending upon their existing prescribed pain treatment, patients received titrated analgesia in a stepped approach. Patients previously receiving no or low dose of acetaminophen received acetaminophen orally (3 g/day) (step 1). If they already had a prescription of acetaminophen, they were adjusted to either extended release morphine orally (10 or 20 mg/day) (step 2) or buprenorphine transdermal patch (5 μg or 10 μg/h for 7 days) (step 3). If patients were already receiving step 3 medications and had neuropathic pain, they received pregabalin orally (25, 50 or 75 mg/day) (step 4), using a fixed dose regime throughout the 8-week treatment period. Most cases at steps 2–4 received combination therapy with different analgesics. Patients with swallowing difficulties started at step 3. Medication was offered at breakfast, lunch and dinner (approximately 08:00, 13:00 and 18:00 h), respectively. In patients who were not

able to tolerate this treatment, the dosage was reduced or the patient was withdrawn from the study and treated as clinically appropriate. The treating physicians were instructed to keep prescriptions and doses of analgesics unchanged in the control group.

2.4 Outcome measures

Outcome measures were completed at baseline, 2, 4, 8 and 12 weeks. The MOBID-2 Pain Scale was used to assess pain intensity in the participants. MOBID-2 is a two-part staff-administered observational pain behaviour instrument, developed and tested in NH patients with advanced dementia (Husebo et al., 2010). Assessment of pain intensity is based upon the patient's immediate pain behaviour such as vocalization, facial expression and use of defensive body positions. MOBID-2 part 1 assesses pain related to the musculoskeletal system in connection with standardized, guided movements during morning care (five items). MOBID-2 part 2 assesses pain that might originate from internal organs, head and skin and is monitored over time (five items). After registration of pain behaviour, observations are inferred to pain intensity using a 10-point numerical rating scale (NRS). Caregivers are encouraged to judge whether the observed behaviour is related to pain or to dementia and psychiatric disorders. Finally, an independent overall pain intensity score is completed, again using a NRS. Previous studies on the psychometric properties of MOBID and MOBID-2 pain scale have showed that the inter- and intra-rater and test–retest reliability of the scale is very good to excellent, with Intra Class Correlations ranging from 0.80 to 0.94 and from 0.60 to 0.94, respectively (Husebo et al., 2007, 2009, 2010). Internal consistency was highly satisfactory with Cronbach's α ranging from 0.82 to 0.84. Face, construct and concurrent validity was good and it has shown good feasibility in clinical practice (Husebo et al., 2007, 2009). Indications were provided that MOBID-2 is responsive to a decrease in pain intensity after pain treatment (Husebo et al., 2014).

An additional outcome measure was physical function assessed with the Barthel ADL index (range 0–20), in which higher values indicate higher levels of activities of daily functioning and independence (Mahoney and Barthel, 1965). Safety and tolerability were monitored at each assessment, and all adverse events and vital signs were recorded.

2.5 Randomization and blinding

Randomization was executed using Stata version 8 (Stata-Corp LP, College Station, TX, USA). To eliminate selection bias at institution level, we defined a cluster as a single independent NH unit (with no crossover of staff), and randomized these units. Thus, patients in each cluster were randomly assigned to receive SPTP in the intervention group or continue with treatment as usual (control group), using a computer-generated list of random numbers for allocation of the clusters by the study statistician. During enrolment, two trained research assistants interviewed the patients' primary

caregivers. The outcome measures and drug prescriptions were reviewed by a consultant for old age psychiatry (D.A.), an anaesthetist and pain therapist (B.S.H.), one of the research assistants (R.S.) and a senior member of staff, usually a general practitioner from the NH after completion of the enrolment process and prior to randomization. Researchers and nurses with responsibility for carrying out the intervention did not participate in data collection. Research assistants and staff members who collected the data were blinded to group allocation and type of intervention during the study period. The staff were instructed not to discuss management procedures.

2.6 Data analysis

The mean, standard deviation (SD) and range were calculated for participant demographics. We described the groups at baseline with two-sample independent t-tests for normally distributed continuous variables, chi-square test for categorical variables and Mann–Whitney test for continuous variables with non-normal distribution. Differences in mean and standard error (SE) of the mean MOBID-2 Pain Scale and ADL scores over time between treatment groups were estimated with linear random intercept quantile mixed-effect models. Mixed model regression modelled with linear random intercept permits multiple measurements per person over time, irregular intervals between measurements and allows for incomplete data on assumption that data are missing at random (Verbeke and Molenberghs, 2000). We included the NH units as a nestling level in our analysis. Statistical analyses were conducted with IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY, USA) and R version 3.0.0 (The R Foundation for Statistical Computing, Vienna, Austria) and package nlme-3.1-109.

3. Results

3.1 Cohort characteristics

Four hundred twenty eligible patients were identified, of whom 352 were included and cluster randomized to control ($n = 177$, cluster $n = 27$) or intervention groups ($n = 175$, cluster $n = 33$). In total, 327 participants had a MOBID-2 pain score at baseline and were included in this stepwise protocol of treating pain analyses (control $n = 163$, intervention $n = 164$). Dropout rate was equally distributed between groups. The detailed flow of participants through this study is summarized in Fig. 1. Demographic data for the cohort are presented in Table 1. No differences were found between the groups at baseline.

Pain diagnoses and intensity were distributed equally between control and intervention groups at baseline. Over 70% of participants had one or more diagnoses of pain (Table 1). Inferred pain intensity greater than zero was observed in over 80% of the patients ($n = 282$), and intensity of 3 or higher was seen in over 60% ($n = 203$). MOBID-2 part 1 assessment indicated that the majority of pain resulted from guided movements of the legs and from turning over in bed. MOBID-2 part 2 showed the most frequently affected sites were the pelvis/genital organs and skin (Table 2). We found no differences in pain intensity between groups with different levels of dementia assessed by MMSE ($p = 0.196$). Participants who were assumed to have neuropathic pain and were treated with pregabalin had significantly higher pain scores than controls and the other treatment groups at baseline (MOBID-2 pain score 6.1; $p = 0.001$). Pain intensity did not differ between the other groups at baseline: control group (MOBID-2 pain score 3.65), acetaminophen group (mean 3.53; $p = 0.674$) and morphine group (extended release morphine and buprenorphine) (mean 3.97; $p = 0.469$).

3.2 SPTP treatment allocation

In the intervention group, 62.8% of the patients ($n = 103$) started administration of acetaminophen (step 1) (i.e., acetaminophen 3 g/day), and 5.5% ($n = 9$) had an existing prescription of lower dose acetaminophen increased to a higher dosage. Thus, 112 patients received acetaminophen only. Three patients received step 2, all three had acetaminophen as well (two started with extended release morphine, and in one participant the primary prescription was adjusted). Step 3, the buprenorphine transdermal patch, was administered to 29 patients (17.7%), and the buprenorphine dosage was increased in an additional eight participants. In total, 37 participants were treated with buprenorphine transdermal patch, of whom 9 received the patch alone, with no other medication, due to swallowing issues. Twelve participants were treated with step 4, pregabalin, all of whom also received acetaminophen and the buprenorphine patch. All other patients ($n = 28$) had a combination of acetaminophen and buprenorphine.

3.3 Outcome measures

Analysis of pain intensity outcomes showed a significant improvement in the treatment group compared to controls in weeks 2 [average treatment effect (ATE) −0.703; SE 0.24; $p = 0.004$] and 8 (ATE = −1.393; SE 0.3; $p < 0.001$) (Table 2). This improvement was seen in MOBID-2 overall pain intensity (Fig. 2) in addition to specific items assessing musculoskeletal pain (Fig. 3) and pain related to internal organs, head and
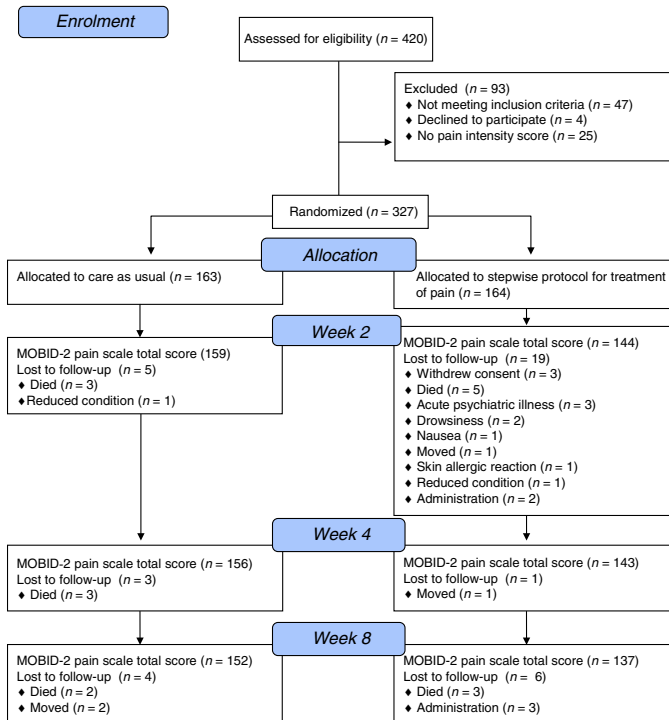
Figure 1 Flow chart showing patients flow through the 12-week study period including control and intervention groups.

skin (Fig. 4). A sub-analysis of the participants who had a score of 3 or greater on the MOBID-2 Pain Scale at baseline also showed significant benefit in the treatment group compared with control (ATE = −1.739; $p < 0.001$) in week 8, with an average difference in pain reduction of 50% from baseline to week 8 in the treatment group.

An analysis of the efficacy of different treatment approaches within the treatment group is presented in Fig. 5 and shows that participants treated with acetaminophen had significant improvement of pain at all time points, at week 2, 4 and 8, respectively (ATE = −0.67, $p = 0.010$; ATE = −0.92, $p < 0.001$; ATE = −1.30, $p < 0.001$). Patients treated with extended release morphine or buprenorphine transdermal patch also showed a significant decrease in MOBID-2 total scores, but not before week 8 (ATE = −1.14; $p = 0.008$). Patients treated with pregabalin had a clinically and statistically significant effect after 4 weeks (ATE = −1.8; $p = 0.016$) and showed a 61.7% reduction in pain from baseline to week 8 (ATE = −3.53; $p < 0.001$) compared with the control group. All participants treated with analgesia

experienced worsening of pain following discontinuation of treatment during the washout period (acetaminophen: ATE = −0.76, $p = 0.004$; morphine or buprenorphine: ATE = −0.223, $p = 0.075$ pregabalin: ATE = −1.438, $p = 0.075$) (Fig. 5).

As previously reported (Husebo et al., 2011), no significant differences were seen in ADL between intervention and control groups at week 8 ($p = 0.443$). However, a sub-analysis of the acetaminophen group demonstrated improved ADL from baseline in the intervention group (ATE = +1.00; $p = 0.022$) at week 8 compared with the control group (Fig. 6). Entering NH unit as a nestling level did not alter our findings.

3.4 Adverse events

Adverse events related to pain treatment interventions were registered for six patients (nausea $n = 1$, rash from patch $n = 1$, reduced appetite $n = 2$, somnolence/drowsiness $n = 2$). Most patients had acetaminophen ($n = 120$), but few left the study due to side effects ($n = 2$). Twice as many left from the opioid group ($n = 4$), although this group counted only 33% com-

Table 1 Demographic and clinical characteristics of the study population. Variables reported as mean (SD), medians (SE) and proportions (%).

Characteristic	Control mean (SD) $n = 163$	Intervention mean (SD) $n = 164$	p
Age[a]	86.4 (6.7)	85.2 (7.0)	0.102
Women (%)[b]	131 (74.0)	131 (74.9)	0.856
MMSE[c,d]	8.9 (6.6)	7.6 (6.6)	0.065
Barthel ADL index[c,e]	8.7 5.5)	7.8 (5.6)	0.148
MOBID-2 Pain Scale[c,f]	3.7 (2.5)	3.8 (2.7)	0.988
MOBID-2 Pain Scale ≥ 1[c]	4.2 (2.2)	4.5 (2.4)	0.273
MOBID-2 Pain Scale ≥ 2[c]	4.5 (2.1)	4.9 (2.2)	0.213
MOBID-2 Pain Scale ≥ 3[c]	5.3 (1.8)	5.4 (2.0)	0.830
No pain diagnoses in total (%)[c]	29.4	29.4	0.823
1 pain diagnoses (%)	30.8	30.3	
2 pain diagnoses (%)	24.4	22.6	
≥3 pain diagnoses (%)	16.0	18.1	
Old fracture (%)[b]	27.6	27.1	0.801
Arthritis (%)[b]	22.4	20.0	0.600
Osteoporosis (%)[b]	20.5	23.9	0.477
Heart (%)[b]	17.9	15.5	0.561
Cancer (%)[b]	16.7	20.0	0.448
Neuropathy (%)[b]	1.9	4.5	0.196
Wound gangrene (%)[b]	1.3	3.9	0.150
Muscle spasm (%)[b]	1.3	2.6	0.406

MMSE, Mini-Mental State Examination (scores from 0 to 30); ADL, activities of daily living (scores 0–20); MOBID-2, Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale.
[a]t-Test for continuous variable, normally distributed.
[b]Chi-square test for dichotomous categorical variables.
[c]Mann–Whitney U for unequal distributed continuous variable given in medians (SE). Variables reported as mean (SD) and median (%) if not indicated otherwise.
[d]Lower scores indicate more cognitive impairment.
[e]Higher scores indicate better function.
[f]Higher scores indicate more pain (scores ≥ 3 accepted as clinically relevant).

pared with the acetaminophen group. Pregabalin was given to 12 patients and 2 left the study. Fourteen deaths occurred during the 8-week study, of which six were participants in the intervention group.

4. Discussion

Pain is a clinically significant issue in dementia and is known to be related to the development of challenging symptoms such as BPSD and to have a significant impact on the quality of life and well-being. This article reports the first study to specifically measure the effect of pain treatment on the intensity of pain in people with dementia living in NH. This secondary analysis has shown that a stepwise approach to treating pain, which is tailored to the individual and adapted according to the patients' ongoing pain

medication, significantly improved overall pain intensity in residents with moderate and severe dementia as measured by the MOBID-2 Pain Scale. Pain intensity was reduced by 45% in the intervention group after 8 weeks of treatment. All treatments resulted in benefit at the 8-week time point, with pregabalin also conferring effective pain relief by week 4, and acetaminophen providing benefit after 2 weeks. Importantly, all participants receiving analgesia experienced a significant worsening of pain when treatment was discontinued at the end of the trial. In addition to the impact on pain intensity, the study also found a significant improvement in physical function in participants receiving acetaminophen at 8 weeks. Pain is known to influence mobility and ability to perform daily tasks, and this is an important outcome. Since individuals receiving acetaminophen within step 1 of the SPTP for the full 8 weeks were predominantly experiencing mild or moderate pain, this finding indicates the additional value of analgesia for these individuals. Taken together, these findings clearly indicate the value of prompt and ongoing analgesic treatment in people with dementia where it is clinically appropriate.

Clinical guidelines for older adults have been published by the AGS panel from 1998, with regular updates in 2002 and 2009 (AGS Panel on Persistent Pain in Older Persons, 2009). The latest version also includes recommendations for accurate pain assessment in patients with dementia. However, guidelines for treatment of pain in patients with dementia are still urgently needed. We applied the recommendations from the AGS panel guidelines and focused upon titration and combination of two or more drugs with complementary mechanisms to attain improved pain reduction with less hepatic and kidney toxicity and adverse effects. Following the recommendations for clinicians, we used a maximum safe dose (<4 g/24 h) of acetaminophen for our patients (AGS Panel on Persistent Pain in Older Persons, 2009).

To our knowledge, this is also the first RCT to evaluate the anti-epileptic pregabalin to specifically treat neuropathic pain in patients with dementia. Treatment followed recommendations by the AGS panel, starting on low doses (25 mg/day), increasing to 75 mg/day where necessary. Pregabalin selectively binds to voltage-gated calcium channels in the brain and spinal cord and has been shown to decrease the release of excitatory neurotransmitter and reduce calcium channel function (Dooley et al., 2000; Fehrenbacker et al., 2003; Micheva et al., 2006). Pregabalin has shown initial benefit in an RCT of painful diabetic neuropathy (Rosenstock et al., 2004). Despite

Table 2 Efficacy of treating pain on different locations of pain with the sum scores of musculoskeletal pain (MOBID-2 part 1) and pain from internal organs head and skin (MOBID-2 part 2) between control group and treatment group at baseline and in week 8 (n = 327).

Pain location	Control (n = 163)			Intervention (n = 164)			df[a]	t[a]	p[a]
	Baseline mean (SE)	Week 8 mean (SE)	Difference	Baseline mean (SE)	Week 8 mean (SE)	Difference			
Hands	0.8 (0.2)	1.0 (0.1)	0.161	1.1 (0.2)	0.8 (0.2)	−0.243	1183	−2.457	0.014
Arms	1.7 (0.2)	1.8 (0.2)	0.119	1.8 (0.2)	1.2 (0.2)	−0.677	1180	−2.868	0.004
Legs	2.6 (0.2)	2.2 (0.2)	−0.342	2.0 (0.2)	1.6 (0.2)	−0.375	1174	−0.177	0.859
Turn over	1.9 (0.2)	2.0 (0.2)	0.026	2.0 (0.2)	1.3 (0.2)	−0.739	1156	−2.665	0.008
Sit	1.6 (0.2)	2.0 (0.2)	0.398	2.1 (0.2)	1.2 (0.2)	−0.826	1154	−4.498	<0.001
Part 1 total score	8.7 (0.8)	8.9 (0.7)	0.393	9.0 (0.8)	5.8 (0.8)	−3.233	1132	−3.567	<0.001
Head, mouth, neck	1.0 (0.1)	0.9 (0.1)	−0.091	1.4 (0.2)	0.8 (0.1)	−0.627	1184	−2.548	0.011
Heart, lung, chest	0.8 (0.2)	0.8 (0.1)	0.049	0.8 (0.1)	0.4 (0.1)	−0.426	1182	−2.675	0.008
Abdomen	0.9 (0.1)	0.7 (0.1)	−0.143	1.0 (0.2)	0.4 (0.1)	−0.546	1182	−1.823	0.069
Pelvis, genital organs	1.6 (0.2)	1.6 (0.2)	−0.023	1.8 (0.2)	0.8 (0.2)	−0.944	1182	−3.276	0.001
Skin	1.7 (0.2)	1.4 (0.2)	−0.208	1.5 (0.2)	1.0 (0.2)	−0.570	1184	−1.458	0.145
Part 2 total score	5.9 (0.5)	5.4 (0.4)	−0.416	6.5 (0.5)	3.4 (0.4)	−3.113	1177	−3.766	<0.001
Overall pain intensity	3.7 (0.2)	3.4 (0.2)	−0.297	3.8 (0.2)	2.1 (0.2)	−1.655	1123	−5.277	<0.001

df, degree of freedom; SE, standard error.
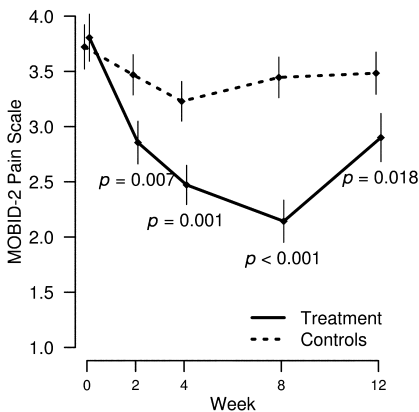Part 1 = musculoskeletal pain.
Part 2 = pain related to internal organs head and skin.
[a]Random-intercept model in a two-way repeated-measure configuration.

only 12 participants receiving pregabalin, the data indicate significant benefit. This finding is of particular importance due to the frequency of central neuropathic pain in people with dementia associated with white matter lesions in people who have experienced a stroke (Scherder et al., 2003; Scherder and Plooij, 2012). Studies also indicate the presence of neuropathic pain in people with vascular dementia, mixed dementia, Alzheimer's disease and frontotemporal

dementia as a result of specific neuropathology (Scherder et al., 2003; Rosenstock et al., 2004; Husebo et al., 2008; Scherder and Plooij, 2012). Furthermore, diabetes is particularly common among people with dementia and is associated with considerable neuropathic pain (Wild et al., 2004; Zilliox and Russell, 2011). Pregabalin therefore warrants further investigation as an analgesic treatment option for this group.

Our dataset has revealed valuable data regarding the specific tolerability of different pharmacological treatments for pain in this patient group. The largest proportion of participants in the trial who received treatment was prescribed with acetaminophen. This

Figure 2 MOBID-2 Pain Scale total score with mean and standard error of the mean by control and treatment group over study period in total study sample.
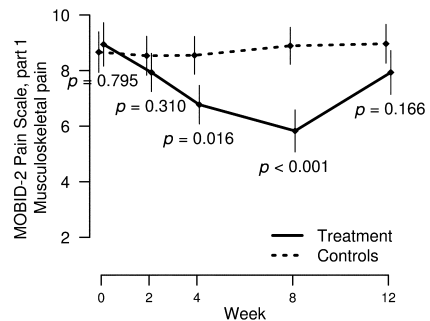
Figure 3 Mean and standard error of the mean in musculoskeletal pain (MOBID-2 Pain Scale part 1) scores by control and intervention groups over study period.
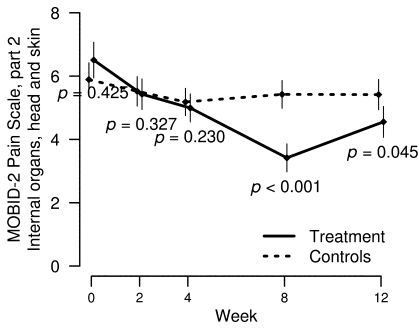
Figure 4 Mean and standard error of the mean in pain related to internal organs, head and skin (MOBID-2 Pain Scale part 2) by control and intervention groups over study period.

treatment was extremely well tolerated. Only 2 of 120 patients left the study, both because patient's relatives withdrew consent. Acetaminophen is therefore both effective and very well tolerated by people with dementia, confirming the suitability of this agent as a first-line analgesic. Forty participants received an opioid analgesic (extended release morphine or buprenorphine transdermal patch), of whom four withdrew due to possible side effects (femur fracture, drowsiness and nausea, local reaction to the transdermal patch, appetite and eating disturbances). This
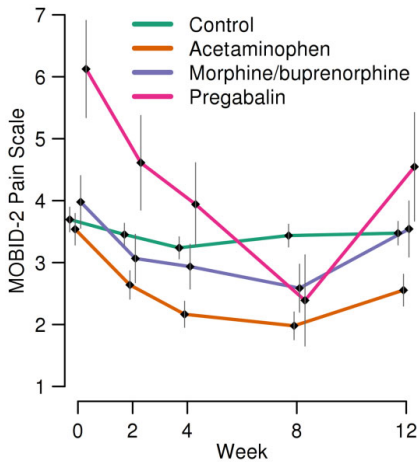

Figure 5 MOBID-2 Pain Scale total score with mean and standard error of the mean, ordered by different analgesics (acetaminophen, extended release morphine and buprenorphine transdermal patch and pregabalin) and control group over study period.
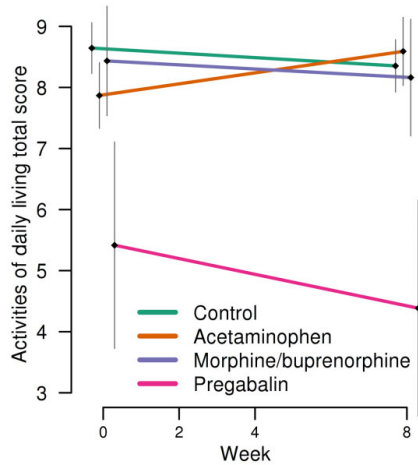

Figure 6 Activity of daily living total score with mean and standard error of the mean, in order to different analgesics (acetaminophen, extended release morphine and buprenorphine transdermal patch and pregabalin) and control groups over study period.

outcome reflects the literature, which indicates that the opioid drug class is generally well tolerated with the most common adverse drug reactions being arrhythmia (12.1%), pruritus (10.5%), nausea (9.2%) and dizziness (4.6%) (Hamunen et al., 2008; Huang and Mallet, 2013), in addition to an increased risk of falls and hip fractures (Deandrea et al., 2010). While buprenorphine appears to be safe in people with renal impairment, it should be noted that due to the metabolic pathway of this agent, careful monitoring is required in people with hepatic impairment, and this is an important consideration when prescribing to people with dementia. The only previous RCT of an opioid for pain in dementia reported a high 47% dropout rate (Manfredi et al., 2003). Our study has demonstrated efficacy and improved tolerability with buprenorphine administered through transdermal patches, which are already in use to treat chronic nociceptive, neuropathic and cancer-related pain (Pergolizzi et al., 2010). Following recommendations by the AGS panel to keep stable blood levels, 12 patients received the buprenorphine patch only, as they already were on a strong morphine option and had swallowing difficulties.

The late-onset effect of buprenorphine transdermal patch after 8 weeks was an unexpected finding. Cognitive function and ADL function were stable over the period, suggesting that reduced pain was a treatment effect and not related to sedation. The lower tolerabil-

ity of opioids in people in dementia indicates the need for an intermediate analgesic as an alternative to escalation to opioids where acetaminophen is not sufficient. There are both benefits and harms associated with the use of non-steroidal anti-inflammatory drugs (Huang et al., 1999; Bannwarth, 2008), and a further evaluation of this analgesic group could be of value in informing the management of pain in people with dementia in the future.

Withdrawal among participants receiving pregabalin was relatively high in this study, with 2 of 12 participants withdrawing due to somnolence, nausea and drowsiness. This occurred despite the lower dosage used in the study (25 mg) compared with the recommended daily dose of 150 mg used in younger individuals where the safety profile is very good. This provides the first safety data for pregabalin in this patient group. However, our results have to be controlled by a clinical trial with appropriate sample size.

To date, the prevalence of pain in people with dementia in NH has not been fully established. While it was not the primary purpose of this study, baseline data indicate that almost 60% of these individuals were experiencing significant pain, with a pain score of at least 3. Furthermore, almost 70% had one or more diagnoses of pain, indicating an extensive prevalence of pain. The pattern of prescribing within the SPTP also indicates that many individuals were receiving suboptimal analgesia prior to the study commencing, most likely due to undiagnosed mild or moderate pain. These secondary findings provide further weight to the need for more effective identification of pain in dementia through an accurate and easily implementable assessment and monitoring tool. The MOBID-2 Pain Scale utilized in this study has shown excellent reliability and sensitivity to date, and this study further confirms its utility in research. It will now be essential to further establish its use in clinical practice in order to provide health-care professionals with adequate knowledge, as well as an effective pain assessment (Pieper et al., 2013).

This is the largest study to have investigated the effect of pain treatment on pain intensity in people with dementia living in NH. It has provided robust, well-powered and clinically meaningful data that demonstrate the efficacy of a stepped pharmacological treatment approach in this patient group. A possible limitation in this study may be the heterogeneous nature of the dementia cohort as no definition was made of the sub-types of dementia within the participants. However, due to the frequent absence of a differential diagnosis in people with dementia in NH, it is more meaningful to consider treatment effects in this group since it is representative of the current clinical situation and will provide information that can be directly translated to guidance for practice. The data provide robust data for the overall cohort. Efficacy data for the individual pharmacological agents are necessarily derived from smaller groups of participants due to the stepped nature of the intervention. It would therefore be a valuable next step to evaluate each of the agents in larger cohorts to confirm the efficacy demonstrated in this study. Further evaluation of alternative treatment options such as anticonvulsants, antidepressants and novel analgesics is also urgently needed in order to establish the most effective stepwise treatment regimen for this patient group.

Author contributions

Acknowledgements

Clinical study registration

The trial is registered at ClinicalTrials.gov (NCT01021696) and at the Norwegian Medicines Agency (EudraCT nr 2008-007490-20).

Ethical approval

Regional Committee for Medical Ethics, Western Norway (REK-Vest 248.08).

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Paper II

II

Paper III

III

Original Study

Signs of Imminent Dying and Change in Symptom Intensity During Pharmacological Treatment in Dying Nursing Home Patients: A Prospective Trajectory Study

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ABSTRACT

Objectives: To investigate whether it is possible to determine signs of imminent dying and change in pain and symptom intensity during pharmacological treatment in nursing home patients, from day perceived as dying and to day of death.
Design: Prospective, longitudinal trajectory trial.
Setting: Forty-seven nursing homes within 35 municipalities of Norway.
Participants: A total of 691 nursing home patients were followed during the first year after admission and 152 were assessed carefully in their last days of life.
Measurements: Time between admission and day of death, and symptom severity by Edmonton symptom assessment system (ESAS), pain (mobilization-observation-behavior-intensity-dementia-2), level of dementia (clinical dementia rating scale), physical function (Karnofsky performance scale), and activities of daily living (physical self-maintenance scale).
Results: Twenty-five percent died during the first year after admission. Increased fatigue (logistic regression, odds ratio [OR] 1.8, $P = .009$) and poor appetite (OR 1.2, $P = .005$) were significantly associated with being able to identify the day a person was imminently dying, which was possible in 61% of the dying (n = 82). On that day, the administration of opioids, midazolam, and anticholinergics increased significantly ($P < .001$), and was associated with amelioration of symptoms, such as pain (mixed-models linear regression, 60% vs 46%, $P < .001$), anxiety (44% vs 31%, $P < .001$), and depression (33% vs 15%, $P < .001$). However, most symptoms were still prevalent at day of death, and moderate to severe dyspnea and death rattle increased from 44% to 53% ($P = .040$) and 8% to 19% ($P < .001$), respectively. Respiratory symptoms were not associated with opioids or anticholinergics.
Conclusion: Pharmacological treatment ameliorated distressing symptoms in dying nursing home patients; however, most symptoms, including pain and dyspnea, were still common at day of death. Results emphasize critical needs for better implementation of guidelines and staff education.
Trial registration: ClinicalTrials.gov NCT01920100.

The rapidly aging population, combined with substantial urban changes in the society, makes the role of institutional care increasingly important for the dying old. Every year, approximately 20% of all dying UK citizens[1] and almost 50% of the dying Norwegian population, die in a nursing home.[2]

More than 80% of all nursing home patients have dementia, a chronic, usually progressive and incurable disease, with increased risk of neuropsychiatric symptoms and mortality.[3,4] To enhance advance care planning and end-of-life care in nursing homes, mid- and short-term prognostication[5] and pain and symptom management are key responsibilities for the clinician.[6,7] According to the newest National Institute for Health and Care Excellence (NICE) guidelines, *Care of dying adults in the last days of life*, the recognition and weighing up of factors that may indicate that someone is imminently dying are complex and underestimated.[8] Challenges are even more urgent in nursing home patients and people with dementia.[9] Mitchell et al[10] demonstrated that pneumonia, repeated episodes of fever, and eating problems increased the 6-month mortality risk in people with dementia. In the last 3 months of life, dyspnea, pain, and pressure ulcers were identified to be the most common and distressing symptoms in these individuals. However, many nursing home patients die unexpectedly and suddenly because signs and symptoms for prognostication of the imminent death are not yet established, leading to increased

suffering of the individual.[11] A Dutch observational study reported that identifying a patient as terminally ill was possible only when the person died within the next 3 days.[12] Patients in this study were recognized as imminent dying by the lack of fluid and nutrition intake, general weakness, dyspnea, and somnolence. Another nursing home study found significant decrease of pain and distressing symptoms during the last 2 days of life, by retrospective observation.[13] Contrary to these findings, pain, agitation, and dyspnea were found in 6% to 71% of affected patients, in the last week and days before death.[14]

Better predictability and treatment of these symptoms may contribute to the overall end-of-life care in nursing homes, and most recent recommendations emphasized the importance of prospective studies in elderly patients and people with dementia.[15] Few studies have, however, assessed prospectively the change of pain and symptom intensity alongside pharmacological treatment, from the day when the patient was imminently dying and to the day of death.

We identified, prospectively, typical signs and symptoms prevalent on the day when the patient was imminently dying and the day of

Table 1
Measurement Tools Used in the Study

	What Does the Tool Measure?	Tool Characteristics and Psychometric Properties	Time Point for Measurement
ESAS	Pain and distressing symptoms (fatigue, drowsiness, nausea, appetite disturbances, dyspnea, depression, anxiety, and well-being)	Edmonton symptom assessment system (ESAS) evaluates subitem intensity on an 11-point Likert scale (range 0–10). Intensity is grouped as none to mild (0–2), mild to moderate (3–6), and moderate to severe (7–10).[37] ESAS has shown good psychometric properties, and has been used in dying people with dementia.[15–17]	Baseline
ESAS	Pain and distressing symptoms (fatigue, drowsiness, nausea, appetite disturbances, dyspnea, depression, anxiety, sleep, vomiting, delirium, agitation, death rattle, and constipation)	ESAS evaluates subitem intensity on an 11-point Likert scale (range 0–10). Intensity is grouped as none to mild (0–2), mild to moderate (3–6), and moderate to severe (7–10).[37] ESAS has shown good psychometric properties, and has been used in dying people with dementia.[15–17]	Day perceived as dying, day of death
CDR	Cognitive staging tool	Clinical dementia rating (CDR) consists of 5 steps (0–3) distributed as follows: no dementia (0 and 0.5), mild dementia (1), moderate dementia (2), severe dementia (3). CDR is a reliable, valid, and feasible tool, validated in the Norwegian language.[27]	Baseline
KPS	Functional performance status	Karnofsky performance status scale (KPS) is an 11-step rating scale from normal function (100), to dead (0). KPS demonstrates good psychometric properties in patients with cancer and in elderly people.[21]	Baseline, day perceived as dying
MMSE	Cognitive staging tool with 8 domains (orientation to time and place, short-term recall, attention, and calculation, long-term recall, language, repetition, and complex commands)	Mini-mental state examination (MMSE) is a 30-point questionnaire (0–30); severe impairment (0–11), moderate impairment (12–17), mild impairment (18–23), and no impairment (24–30). MMSE is widely used and demonstrates good validity and reliability.[23–26]	Baseline
MOBID-2	Pain intensity and pain location from musculoskeletal pain (Part 1), and pain from internal organs, head, and skin (Part 2)	Mobilization-observation-behavior-intensity-dementia-2 Pain Scale (MOBID-2) assesses pain intensity and pain location based on patient's pain behavior during standardized, guided movements. The 10 items are scored on a 0–10 numerical rating scale (0 = no pain, 10 = severe pain). Based on all observations, the patient's overall pain intensity is rated again on a 0–10 scale. MOBID-2 has excellent reliability, validity, and good responsiveness.[18]	Baseline, day perceived as dying day of death
PSMS	Activities of daily living are assessed by 6 domains (toileting, eating, dressing, grooming, transfer, and bathing)	Lawton and Brody physical self-maintenance scale (PSMS) has 6 domains, each scored on a scale from 1–5 (range 6–30). Increasing numbers means increasing dependence in daily functioning. Good reliability and validity, and sensitive to change in severe dementia.[19,20]	Baseline
RAI-PC	Distressing symptoms, care and treatment provided	Residents Assessment Instrument for Palliative Care (RAI-PC) consists of 8 domains (symptoms, communication, mood, functional status, preferences, social relations, spirituality, and treatments), of which we included items for mouth care, bedsores, and nutrition.[22]	Baseline, day perceived as dying, day of death

Enrolment

Enrolled when admitted to the NH (n=691)

Excluded (n=84)
♦ Moved home or another institution (n=41)
♦ Withdraw consent (n=6)
♦ Not admitted for at least one year (n=37)

Patients followed individually (n=607)

Died the first year (n=152)

Continues in study after one year (N = 455) (i.e. followed until 25.01.2015)

Not assessed (n=18)

Assessed at day of death (n=134)
♦ Assessed at day perceived as dying (n=82)
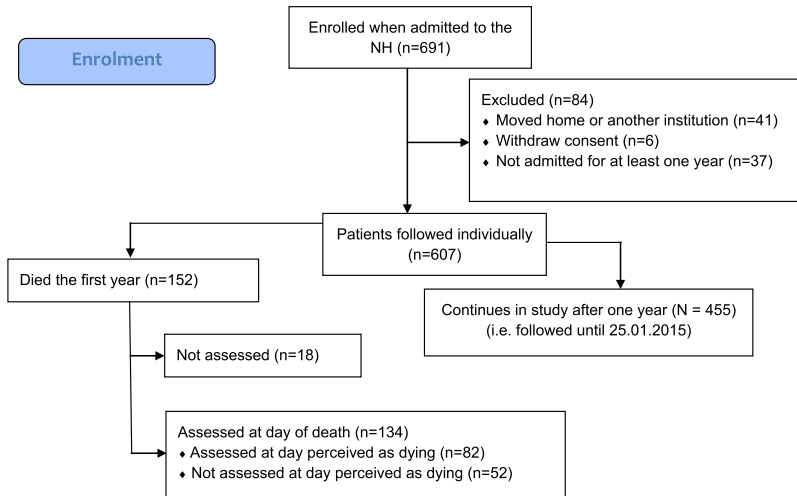♦ Not assessed at day perceived as dying (n=52)

Fig. 1. Study flow chart for 691 patients individually admitted to 47 Norwegian nursing homes (NH) from January 2012 to June 2014.

death. Further, we investigated whether opioids, anxiolytics, and anticholinergics were associated with change of pain and symptom intensity between these 2 time points.

Methods

This was a prospective, multicenter longitudinal trajectory study including 47 nursing homes from 35 municipalities, in 4 counties of Norway. Between January 2012 and June 2014, eligible participants, aged 65 years and older or younger people with an early diagnosis of dementia, were included. They were all admitted to long-term care units and had an expected survival of 6 weeks or more as judged by the multidisciplinary team (responsible nursing home physician, the responsible nurse, and the primary caregiver). Data were collected for each patient individually, at admission to the nursing home (baseline), at the day the person was perceived as dying (imminent dying), and at the day of death. In our analyses, we included only patients followed for at least 1 year until January 1, 2015, or until death.

Registered nurses and licensed practical nurses (usually the primary caregiver) with close knowledge of the patient performed all assessments under supervision by experienced research nurses. When a patient was not able to give valid self-report due to dementia or unconsciousness, the primary caregiver performed as a proxy-rater. The assessors participated in a 2-day standardized training program (12 hours) and received specific training in use of the instruments, before the data collection. End-of-life care was performed according to standard procedures at each individual nursing home. When a patient showed deteriorating health conditions, the multidisciplinary team evaluated whether the individual was imminently dying by clinical signs due to their own clinical experience. On this day and at the day of death, data were compiled in a telephone interview between the patient's primary caregiver and the research nurse, including standardized measurement scales (Table 1).

Pain and distressing symptoms were assessed at baseline (T0), the day a patient was imminently dying (T1), and the day of death (T2), using the Edmonton symptom assessment system (ESAS) with symptoms of fatigue, drowsiness, nausea, poor appetite, dyspnea, depression, anxiety, and well-being.[16] Six additional symptoms (sleep disturbances, vomiting, delirium, agitation, death rattle, and constipation) were also assessed at T1 and T2 (Table 1). Moderate and

severe symptoms on the ESAS scores (score ≥3) were regarded as clinically significant.[17] The scale has been used and validated for proxy-rating,[18] but has not yet been used in dying patients with dementia. We

Table 2
Baseline Clinical Characteristics for Patients Admitted Individually to a Nursing Home From January 2012 to June 2014

Characteristics	Total Sample, n = 607	Dying Within 1 Year, n = 152	Alive ≥1 Year, n = 455	P*
Age, y, mean (SD)	86.3 (7.5)	86.4 (6.9)	86.3 (7.7)	.944
Female, n (%)	388 (63.9)	90 (59.2)	298 (65.5)	.162
KPS (0−100), mean (SD)	54.3 (28.8)	53.9 (53.9)	54.4 (14.0)	.882
MMSE (0−30), mean (SD)	16.2 (6.5)	15.7 (7.0)	16.3 (6.4)	.549
CDR (0, 0.5), n (%)	78 (13.3)	23 (16)	55 (12.4)	.006
CDR (1), n (%)	142 (24.1)	33 (22.9)	109 (24.5)	
CDR (2), n (%)	247 (41.9)	47(32.6)	200 (44.9)	
CDR (3), n (%)	122 (20.7)	41 (28.5)	81 (18.2)	
PSMS (6−30), mean (SD)	15.4 (0.2)	17.3 (4.8)	14.8 (4.3)	<.001
MOBID-2 (0−10), mean (SD)	2.1 (0.1)	2.3 (2.3)	2.0 (2.1)	.199
ESAS symptoms, mean (SD)				
Pain, mean (SD)	2.6 (2.6)	3.1 (2.6)	2.5 (2.5)	.044
Fatigue, mean (SD)	2.9 (2.7)	3.6 (3.1)	2.7 (2.6)	.001
Drowsiness, mean (SD)	2.7 (2.7)	3.6 (2.9)	2.5 (2.5)	.001
Nausea, mean (SD)	0.6 (1.6)	0.8 (1.9)	0.6 (1.5)	.211
Poor appetite, mean (SD)	1.4 (2.5)	2.0 (3.0)	1.2 (2.3)	.003
Dyspnea, mean (SD)	1.3 (2.2)	2.0 (2.8)	1.0 (2.0)	<.001
Depression, mean (SD)	2.4 (2.6)	2.4 (1.9)	2.3 (2.6)	.771
Anxiety, mean (SD)	2.2 (2.8)	2.6 (3.2)	2.1 (2.7)	.088
Well-being, mean (SD)	3.0 (2.5)	3.5 (2.7)	2.9 (2.4)	.019
RAI-PC items, n (%)				
Problems chewing	26 (7.2)	11 (12.1)	15 (5.6)	.037
Problems swallowing	28 (7.8)	12 (13.2)	16 (5.9)	.025
Mouth pain	11 (3.1)	7 (7.7)	4 (1.5)	.003
Nutritional problems	57 (15.8)	19 (20.9)	38 (14.1)	.127
Nutritional substitute	55 (15.3)	22 (24.2)	33 (12.3)	.006
Bedsore, stage 1	41 (12.4)	17 (20.7)	24 (9.6)	.008
Bedsore, stage 2	52 (15.9)	24 (29.6)	28 (11.4)	<.001
Bedsore, stage 3	14 (4.4)	7 (9.3)	7 (2.9)	.017
Bedsore, stage 4	5 (1.6)	1 (1.3)	4 (1.7)	.846

CDR, higher score indicates higher cognitive impairment; ESAS, higher scores indicate more severe symptoms; KPS, lower scores indicate more dependence; MMSE, lower scores indicate more cognitive impairment; PSMS, increasing numbers indicate higher dependency.

*P value from exact χ^2 test for dichotomous variables and otherwise t test comparing those who died within 1 year with those who were alive after 1 year.

also investigated pain (T0, T1, T2) (scores on mobilization-observation-behavior-intensity-dementia-2 [MOBID-2]),[19] activities of daily living (physical self-maintenance scale [PSMS]),[20,21] and physical function by the Karnofsky performance scale (KPS).[22] We further included the items for nutrition, bedsores, and mouth care assessed by the resident assessment instrument for palliative care (RAI-PC).[23] Cognition and level of dementia were assessed by mini-mental state examination (MMSE)[24–27] and clinical dementia rating scale (CDR) at T0.[28] Administered pharmacological treatment and the causes of death were collected from the patients' medical records.

At nursing home admission, verbal and written informed consent was obtained in direct conversations with all cognitively intact patients with sufficient ability to consent. In patients lacking the ability to consent, verbal and written informed and presumed consent was obtained in direct conversation with the patient (if possible) and his or her legal guardian, usually a family member, after explaining the aims and protocol of the study. The study was approved by the Regional Committee for Medical and Health Research Ethics 2011/1738, and registered at clinicaltrials.gov NCT01920100.

Continuous variables were described by means and SDs, and categorical variables by percentages of sample size and χ^2 square test. The change within individuals in continuous variables was analyzed with the paired t test. To examine differences between groups and time points, we also built regression models for repeated measurements with random effects for intercepts: linear mixed model for continuous and multilevel logistic regression for dichotomous outcome variables. We regarded $P < .050$ as significant and $P < .001$ as highly significant. Statistical analyses were conducted with IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY), and STATA/IC 13.1 (Stata Corp, College Station, TX).

Results

In all, 691 patients from 47 Norwegian nursing homes were included for the baseline assessment (T0). Forty-seven patients were excluded from further follow-up testing because they moved home or to other institutions or declined to participate (Figure 1). To avoid noninformative censoring, we also excluded 37 patients with nursing home stay less than 1 year. This left 607 patients for the follow-up analyses, of whom 369 (63%) had moderate to severe dementia according to the CDR scale (Table 2). A total of 152 patients (25%) died during the first year; of those, 18 were excluded from our analyses because of missing data (Figure 1). The remaining 134 patients were all assessed on their day of death (T2). For 82 patients (61%), the multidisciplinary team identified the day of imminent dying (T1), whereas 52 patients were not recognized as dying, in advance. Thus, our analyses comprised 82 patients at T1 and 134 at T2. The median number of days between T1 and T2 was 3 (range 0–73); 63% died between day 0 and 2, 21% died between days 3 and 7, and 15% died on day 8 or more.

Predictors for 1-Year Mortality

Patients (n = 152, 25%) who died during the first year had more dyspnea ($P < .001$), drowsiness ($P = .001$), fatigue ($P = .001$), pain ($P = .044$), and dependency in daily activities ($P < .001$) at admission (T0), and experienced less well-being ($P = .019$) and appetite ($P = .003$), compared with those who were still alive after 1 year (n = 455) (Table 2). These patients had also more chewing and swallowing problems ($P = .037$, $P = .025$, respectively), pain in the mouth ($P = .003$), nutritional substitution ($P = .006$), and bedsores stage 1, 2, and 3 ($P = .008$, $P < .001$, and $P = .017$, respectively). Diagnoses of death suggested that 21% died of pneumonia, followed by heart failure (18%), dementia (15%), stroke (15%), and cancer (7%) or

kidney failure (7%). In 17% of the patients, diagnoses of death were missing for administrative reasons.

Signs and Symptoms of Imminent Dying (T1)

Shown in Table 3, fatigue (99%), drowsiness (98%), and reduced appetite (95%) were the most frequently observed ESAS symptoms with moderate to severe intensity at T1. Moderate to severe pain assessed with ESAS was found in 60% of the patients, highly correlated

Table 3
Proportion of Patients (%) Categorized According to Severity of ESAS Symptoms in Nursing Home Patients at Day of Imminently Dying and Day of Death

Symptoms	Day of Imminently Dying, n = 82		Day of Death, n = 134		P^*
	%	95% CI	%	95% CI	
Pain, 0–10					<.001
0–2	39.7	(29.3–51.2)	54.2	(45.1–63.0)	
3–6	34.6	(24.7–46.0)	32.5	(24.6–41.5)	
7–10	25.6	(17.0–36.7)	13.3	(8.3–20.8)	
Fatigue, 0–10					.001
0–2	1.3	(0.0–0.9)	10.6	(6.2–17.5)	
3–6	17.9	(10.8–28.3)	10.5	(6.2–17.5)	
7–10	80.8	(70.3–88.2)	78.9	(70.6–85.3)	
Drowsiness, 0–10					<.001
0–2	2.5	(0.6–1.0)	12.2	(7.4–19.3)	
3–6	19.2	(11.8–29.7)	11.4	(6.8–18.4)	
7–10	78.2	(67.4–86.1)	76.4	(68.0–83.2)	
Sleep quality, 0–10					<.001
0–2	50	(38.7–61.3)	61.2	(51.4–70.3)	
3–6	31.6	(22.0–43.1)	19.1	(12.9–27.5)	
7–10	18.4	(11.1–29.0)	19.1	(12.9–27.5)	
Nausea, 0–10					<.001
0–2	75.6	(64.7,84.0)	87.7	(80.5–92.3)	
3–6	19.2	(11.8–29.7)	6.6	(3.2–12.7)	
7–10	5.1	(1.9–13.1)	5.7	(2.7–11.7)	
Vomiting, 0–10					<.001
0–2	84.6	(74.6–91.2)	90.2	(83.5–94.4)	
3–6	10.2	(5.1–19.4)	5.7	(2.7–11.6)	
7–10	5.1	(1.9–13.1)	4.1	(1.7–9.5)	
Poor appetite, 0–10					<.001
0–2	5.2	(1.9–13.3)	21.7	(15.4–30.3)	
3–6	6.5	(2.7–14.9)	9.6	(5.3–16.6)	
7–10	88.3	(78.8–93.9)	68.7	(59.5–76.6)	
Dyspnea, 0–10					.040
0–2	56.6	(45.0–67.5)	47.1	(38.3–56.1)	
3–6	22.4	(14.2–33.4)	24.0	(17.1–32.5)	
7–10	21.1	(13.2–31.9)	29.0	(21.5–38.0)	
Depression, 0–10					<.001
0–2	66.7	(55.0–76.6)	84.9	(77.1–90.3)	
3–6	16.0	(9.2–26.4)	8.4	(4.5–15.0)	
7–10	17.3	(10.2–27.9)	6.7	(3.3–13.0)	
Anxiety, 0–10					<.001
0–2	55.8	(44.4–66.7)	69.1	(60.3–76.7)	
3–6	24.7	(16.2–35.8)	15.4	(10.0–23.1)	
7–10	19.5	(12.0–30.1)	15.4	(10.0–23.1)	
Delirium, 0–10					<.001
0–2	84.0	(73.6–90.8)	91.1	(84.4–95.0)	
3–6	8.0	(3.6–16.9)	2.4	(3.3–12.6)	
7–10	8.0	(3.6–17.0)	0.7	(0.1–0.7)	
Agitation, 0–10					<.001
0–2	90.8	(81.6–95.6)	96.7	(91.5–98.8)	
3–6	6.6	(2.7–15.1)	2.4	(0.1–7.0)	
7–10	2.6	(0.6–10.2)	0.8	(0.1–5.7)	
Death rattle, 0–10					<.001
0–2	92.3	(83.7–96.6)	81.5	(73.5–87.4)	
3–6	5.1	(1.8–13.1)	10.4	(6.1–17.3)	
7–10	2.6	(0.6–10.0)	8.1	(4.4–14.5)	
Constipation, 0–10					<.001
0–2	75.6	(64.7–84.0)	91.8	(85.3–95.6)	
3–6	20.5	(12.8–31.2)	7.3	(3.8–13.7)	
7–10	3.5	(1.2–11.5)	0.8	(0.1–5.7)	

*Mixed-models linear regression symptom as dependent variable and time as independent variable

Table 4
Proportion of Patients (%) by Administered Analgesic Drugs at Day of Imminently Dying and Day of Death

Drugs	Day of Imminently Dying, n = 82		Day of Death, n = 134		P^*
	%	95% CI	%	95% CI	
Paracetamol	51.9	40.8−62.7	35.1	27.4−43.6	.445
Weak opioids†	3.7	1.2−11.1	37.3	29.5−45.9	<.001
Strong opioids‡	48.1	37.3−59.2	65.7	57.1−73.3	<.001
Benzodiazepines	23.5	15.3−34.1	13.4	8.6−20.4	.841
Midazolam	8.6	4.1−17.3	17.2	11.6−24.6	<.001
Antiemetics	1.2	1.2−8.5	3.0	1.1−7.8	.174
Anticholinergics§	6.2	2.5−14.2	18.6	12.9−26.3	<.001
Haloperidol	6.2	2.5−14.2	6.0	3.0−11.6	.255

*Mixed-models linear regression symptom as dependent variable and time as independent variable not P value from exact χ^2 test.

†Codeine, tramadol.

‡Morphine, fentanyl, oxycodone, buprenorphine.

§Glycopyrronium bromide, morphine-scopolamine, scopolamine.

with the total scores on the MOBID-2 Pain Scale (Spearman rho correlation 0.618, $P < .001$). Moderate to severe degree of sleep disturbances (50%), anxiety (44%), dyspnea (44%), and depression (33%) were also common at T1.

We entered the variable identified/not identified as imminently dying into logistic regression analyses with all ESAS symptoms at day of death. We found that increased fatigue (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.16−2.85, $P = .009$) and poor appetite (OR 1.2, 95% CI 1.06−1.41, $P = .005$) were significantly associated with being able to identify the day a person was imminently dying; however, symptoms of pain or dyspnea did not contribute to the recognition of imminent dying, and the presence of delirium was associated with not being able to identify a person as dying at T1 (OR 0.6, 95%CI 0.4−0.9, $P = .010$).

Pain and Symptom Intensity at Day of Death (T2)

Moderate and severe degree of fatigue (89%), drowsiness (88%), and reduced appetite (78%) were still most frequently observed at T2 (Table 3). We found a proportional amelioration in patients with pain (60% vs 46%, $P < .001$), anxiety (44% vs 31%, $P < .001$), depression (33% vs 15%, $P < .001$), nausea (24% vs 12%, $P < .001$), constipation (24% vs 8%, $P < .001$), and delirium (16% vs 3.1%, $P < .001$) from T1 to T2. Dyspnea was frequently observed in the patients, and increased from 44% to 53% ($P = .040$). The proportion of patients with death rattle increased from 8% to 19% ($P < .001$) (Table 3). Between T1 and T2, the prevalence of agitation and delirium together decreased from 28% to 19% ($P < .001$). Patients who in advance were identified as dying (n = 82, 61%) showed significantly more fatigue ($P < .001$), drowsiness ($P = .006$), and loss of appetite ($P < .001$) compared with those who died unexpectedly (n = 52, 39%).

Pain and Symptom Management in the Last Days and Hours of Life

Paracetamol was the most frequently used drug (52%) on day of imminent dying. The administration of strong opioids increased from 48% to 66% ($P < .001$) and weak opioids increased from 4% to 37% ($P < .001$) between T1 and T2. The use of midazolam doubled from 9% to 17% ($P < .001$), whereas anxiolytics, in general, were stable with 29% at T1 and 30% at T2 ($P = .781$). Anticholinergic drug prescription increased from 6% to 19% ($P < .001$), and antiemetics decreased from 15% to 10% ($P = .008$) (Table 4). The linear mixed-models regression analyses investigated changes in ESAS symptom scores only in patients (n = 75) who started pharmacological treatment between T1 and T2 (Table 5). The initiation of opioids was associated with reduced pain intensity ($P = .041$), nausea ($P = .035$), death rattle ($P = .016$), and agitation ($P = .002$), but not dyspnea ($P = .350$). The use of anxiolytics/sedatives was associated with the reduction of nausea ($P = .031$), agitation ($P = .015$), death rattle ($P = .011$), and dyspnea ($P = .007$). Finally, anticholinergics were associated with reduced anxiety ($P = .012$) and agitation ($P < .001$) but not death rattle.

Discussion

This study found that 1 in 4 patients died during the first year after nursing home admission, most often with diagnoses of pneumonia, heart failure, and dementia. The day of imminent dying was identified in 61% by fatigue and poor appetite. In the last days of life, the administration of opioids, midazolam, and anticholinergics increased significantly and was associated with the amelioration of symptoms such as pain, anxiety, and depression.

This was, to our knowledge, the first study that prospectively assessed the change of pain and symptom intensity between the day of imminent dying (T1) and the day of death (T2). Alarming findings uncovered the high number of patients who still experienced dyspnea (53%), pain (46%), sleep problems (40%), and anxiety (31%) at T2. Moreover, the prevalence of death rattle increased from 8% to 19%. Compared with other studies,[11,14] agitation and delirium were less frequently observed at the end of life. It is uncertain, however, whether amelioration of agitated symptoms was related only to the treatment of pain or increased physical weakness over time.[11] A possible under-detection of delirium might limit our results, as we did not include any specific tool assessing this disease by a valid delirium tool, such as the Confusion Assessment Method.[29] Although the administration of opioids increased from 44% to 66% between T1 and T2 in our study, figures were lower in a comparable study in which all patients (100%) received morphine (in mean 30 mg per day).[11] Nuanced interpretation of these results is required because the use of morphine, as a "one-size-fits-all" solution, does not necessarily guarantee good treatment. To validate the efficacy, it is a prerequisite to assess pain and symptom intensity before and after symptom management has been initiated.[30]

Table 5
Change in ESAS Symptom Severity Between the Day of Imminently Dying and the Day of Death

Treatment Symptoms	Opioids, *n = 58			Anxiolytics/sedatives, †n = 27			Anticholinergic drugs, ‡n = 24		
	β	95% CI	P	β	95% CI	P	β	95% CI	P
Pain	−1.04	(−2.03 to −0.04)	.041	−1.00	(−2.50 to 0.54)	.206	−1.45	(−3.02 to 0.12)	.071
Nausea	−0.82	(−1.59 to 0.58)	.035	−0.92	(−1.76 to −0.08)	.031	−1.25	(−2.53 to 0.41)	.058
Death rattle	−1.05	(0.20 to 1.91)	.016	1.96	(0.45 to 3.47)	.011	1.01	(−0.05 to 2.08)	.063
Dyspnea	0.60	(−0.66 to 1 to 86)	.350	2.54	(0.71 to 4.37)	.007	0.15	(−1.74 to 2.03)	.878
Agitation	−1.13	(−1.85 to −0.41)	.002	−0.27	(−2.29 to −0.25)	.015	−2.12	(−3.23 to 0.90)	.001
Anxiety	−1.18	(−2.41 to 0.04)	.058	−0.80	(−2.90 to 1.29)	.451	−2.49	(−4.44 to 0.55)	.012

Only patients who newly started with the treatment were included in these analyses. Investigated with linear mixed-models regression analysis; ESAS subitems as dependent variables.

*Codeine, tramadol, morphine, fentanyl, oxycodone, buprenorphine.

†Benzodiazepines (including midazolam).

‡Scopolamine, morphine-scopolamine, glycopyrronium bromide.

In the present and also other studies,[11,13,14] the most prevalent distressing symptom was dyspnea (53%), complicated by its subjective burden with multiple potential etiologies, such as pneumonia and lung edema in connection to heart failure.[14,31] Although the exact mode of action of opioids in dyspnea management is unknown, peripheral and central mechanisms have earlier been postulated.[32] Thus, it was an unexpected finding that opioids were not associated with reduction of the dyspnea intensity scores in our study. Although it is widely held that glycopyrrolate and scopolamine subcutaneously are useful treatments of death rattle in patients with cancer,[33] it may be difficult for nursing home staff to distinguish between death rattle and sounds of accumulating secretion in connection with pneumonia or heart failure with lung edema.[34] Diagnostic challenges also may be apparent for nausea in connection with newly started opioids in people who are no longer able to describe their suffering. Caregivers in our study observed nausea in only a very few patients; other studies did not mention this symptom.[10,11,14]

Although it is broadly believed that the identification of imminent dying is a hallmark to initiate end-of-life care, the frequency and severity of typical symptoms have not yet been described.[5,35] In the present study, nursing home staff identified T1 in 61% of their patients, through changes in fatigue and poor appetite. Symptoms such as pain, dyspnea, or agitation did not predict imminent death. This is noteworthy because physical symptoms of weakness do not explain the initiation of pharmacological treatment. It is possible that the diagnoses of death (pneumonia, heart failure, and dementia) are trigger factors for increased pain, dyspnea, and anxiety. Interestingly, the prevalence of pain was not associated with agitation in our study, although individual pain treatment has been demonstrated to be correlated to the reduction of pain and agitation.[13,36–38] Compared with younger patients with cancer, the timely prognostication of death is challenging due to the patient's deterioration over a long time period.[35] Our findings should be used to enhance staff education in care of dying nursing home patients because these symptoms are challenging to distinguish: a prerequisite to provide proper symptom management. Although Norwegian authorities are developing a subspecialization for nursing home physicians and a master's degree for geriatric nursing, these standards are not yet established. Regular training and education of nursing home staff and medical students are priorities, but skills and competence regarding end-of-life care in people with dementia vary considerably among institutions.

Limitations and Strengths

Our study used the continuous measures of ESAS symptom scores, which to our knowledge are not validated in dying people with dementia. ESAS has previously been used in the nursing home setting and is the only end-of-life care instrument with relevant symptom list to assess change in symptom intensity during treatment by a continuous scale.[13,39] However, the validity of proxy-rated intensity scores may always be questionable in dying patients and people with dementia. A further limitation is the lack of instruments to assess the quality of life and quality of death and dying, which is an important consideration for future studies. Additionally, to improve the situation for the dying old, we would also recommend exploring convenient nonpharmacological interventions, such as fresh air in the case of dyspnea. Beneficially, our sample size at baseline was larger than comparable studies.[10–14] However, when we assessed the association between newly initiated pharmacological treatment and changes in pain and symptom intensity we ended up with a rather low sample of 75 people.

Conclusion

In the present study, pain and symptom management were associated with symptom relief in dying nursing home patients.

Nevertheless, too many people still experienced unacceptably high levels of pain and distressing symptoms in the last days of life, which emphasizes the critical need for user-specific guidelines, better implementation, and staff education in nursing homes.

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Errata for
Pain and burdensome symptoms in nursing home patients

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Errata

Side 76 I tabell 8 er det satt inn "MOBID-2 Smerteskala" – Det var tidligere utelatt.

Side 21 Figur 1 er erstattet

Side 40 Figur 2 er erstattet

Table 8: Demographic details, physical function, overall pain intensity and prevalence in study samples included in Papers 1 and 3

Characteristics	Paper 1 Pain-BPSD	Paper 2 2000	Paper 3 2011	Baseline REDIC	Imminent dying	Day of death
Age, mean (SD)	85 (7)	84 (7)	86 (8)	86 (8)		
Gender, female %	74	70	71	64		
Dementia, %	87	76	83	87		
ADL function, Barthel mean (SD)[§]	8 (6)					
ADL function PSMS mean (SD)[#]				15 (5)		
Karnofsky (100-0)[†]				54 (30)	16 (10)	
MOBID-2 Smerteskala						
Hands, mean (SD)	0.9 (2.9)			0.4 (1.4)	1.3 (2.6)	0.6 (1.5)
Arms, mean (SD)	1.7 (2.4)			1.0 (2.0)	1.9 (2.5)	1.0 (1.8)
Legs, mean (SD)	2.3 (2.8)			1.3 (2.2)	2.9 (3.1)	1.4 (2.5)
Turn, mean (SD)	2.0 (2.7)			1.2 (2.1)	3.6 (3.2)	2.6 (3.2)
Sit, mean (SD)	1.8 (2.6)			1.1 (1.9)	3.0 (3.2)	0.9 (2.3)
Head, mouth neck, mean (SD)	1.2 (2.1)			0.6 (1.5)	2.0 (3.0)	0.9 (2.0)
Heart, lung, chest, mean (SD)	0.8 (1.7)			0.4 (1.2)	1.1 (2.2)	0.9 (2.0)
Abdomen, mean (SD)	0.9 (1.8)			0.7 (1.6)	1.1 (2.1)	1.0 (1.9)
Pelvis, genital organs, mean (SD)	1.7 (2.6)			1.3 (2.3)	2.3 (2.7)	1.5 (2.3)
Skin, mean (SD)	1.6 (2.4)			0.7 (1.7)	2.0 (3.0)	1.0 (2.2)
Total score, mean (SD)	3.7 (2.6)			2.1 (2.1)	4.0 (3.0)	2.7 (2.8)
Proportion pain 0-2, %	38			63	35	55
Proportion pain 3-6, %	46			33	53	41
Proportion pain 7-10, %	16			4	12	4

[§]ADL scale (0-20): higher score equals better function

[#]ADL scale (6-30): higher score equals more dependence

[†]Higher score equals better function