

Sleep in Nursing Home Patients: Clinical Assessment and the Effects of Pain Treatment on Sleep

Kjersti Marie Blytt

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The work presented in this thesis was conducted between February 2015 and February 2019. The authors contributing to the work are affiliated with the Department of Global Public Health and Primary Care, University of Bergen; the Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital; the Centre for Elderly and Nursing Home Medicine, University of Bergen; and the Department of Clinical Psychology, Faculty of Psychology, University of Bergen.

In 2015, I received a grant from the Western Norway Regional Health Authority (grant number: 911942) to conduct this PhD project. I have since been employed at the Department of Thoracic Medicine, Haukeland University Hospital. During parts of this period, I have been located at the Centre for Elderly and Nursing Home Medicine at the University of Bergen and later at the Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital. In addition, I have been part of the Research Group for General Practice (ALFO), the Research Group at the Centre for Elderly and Nursing Home Medicine (both at the University of Bergen) and the National Research School for General Practice at the University of Oslo. Being part of these groups has allowed me access to a broad and rich scientific environment in which I have presented and discussed the content of this thesis.

During my work with the PhD, my main supervisor has been Elisabeth Flo, Associate Professor at the Department of Clinical Psychology at the Faculty of Psychology, University of Bergen. In addition, I have had two co-supervisors: Bjørn Bjorvatn MD, Professor and Bettina S. Husebo, MD, Professor. Bjorvatn is director of the Norwegian Competence Center for Sleep Disorders (SOVno), Haukeland University Hospital. He has also been the head of the Research Group for General Practice (ALFO), at the Department of Global Public Health and Primary Care, University of Bergen. Husebo is head of the Centre for Elderly and Nursing Home Medicine

(SEFAS) at the Department of Global Public Health and Primary Care, University of Bergen.

My PhD project *Sleep in Nursing Home Patients: Clinical Assessment and the Effects of Pain Treatment on Sleep (SLEEP.PAIN.DEM)* has been part of a larger 13-week, multi-centre, placebo-controlled trial, *Efficacy of Pain Treatment on Depression in Patients with Dementia – A Randomised Clinical Trial of Efficacy (DEP.PAIN.DEM)*. DEP.PAIN.DEM is an international collaborative project, which received funding from the Research Council of Norway (code: 221951). The study is approved by the Regional Committee for Medical Research Ethics (reference number 2013/1474) and the Norwegian Medicines Agency (EudraCT number: 2013-002226-23). In addition to Professor Husebo, the DEP.PAIN.DEM project steering committee includes Professor Dag Aarsland MD, Professor at King's College, London, and Professor Clive Ballard MD, Professor at the University of Exeter Medical School. The study management group includes Associate Professor Elisabeth Flo and Professor Stefan Lautenbacher at the University of Bamberg, who was the head of the former EU-COST-ActionTD1005.

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Abstract

Sleep disturbances, pain and depression are common in nursing home (NH) patients and the assessment and treatment of these conditions are challenging. In this thesis, I aimed to investigate clinical assessment methods of sleep in NH patients, as well as the effects of pain treatment on sleep in NH patients with dementia and depression. The thesis was based on two large-scale studies conducted in Norwegian NHs. In paper 1, we conducted a cross-sectional study (n=83), which investigated the degree to which actigraphy-based and proxy-rater based assessments of sleep in NH patients provide comparable clinical outcomes. We compared the sleep-related items in the Neuropsychiatric Inventory – Nursing Home version (NPI-NH) and the Cornell Scale for Depression in Dementia (CSDD) with actigraphy assessments of sleep disturbances. In papers 2 and 3, we conducted a multicenter, two-armed, double-blinded, placebo-controlled, randomised clinical trial. The present thesis reports secondary outcomes of this RCT and includes papers that aimed to investigate the short-term effects (paper 2) and long-term effects (paper 3) of pain treatment on sleep as measured with actigraphy in NH patients with dementia and depression (n=106).

In paper 1, the CSDD and NPI-NH measures were found to have a very small to small chance of capturing the sleep outcomes identified by actigraphic recordings. We concluded that the usefulness of proxy-rater measures of sleep is unclear, and further research into their clinical value is needed. The results from papers 2 and 3 of the thesis show that active pain treatment improved sleep compared to placebo in the short-term (paper 2). However, no such effect was found in the long term (paper 3). From baseline to week 13 of the treatment period, there was considerable attrition of patients due to adverse events, suggesting that more research into which analgesics may be most suitable in people with dementia is needed. The underlying mechanism of the results from papers 2 and 3 is unknown, and future research should explore this with a different design – using analgesics that patients with dementia and depression tolerate better. Such investigations should also focus on the clinical value of such

treatment. To summarise, the thesis provides insight into strengths and weaknesses of different assessment tools that can be used to assess sleep in NH patients. It moreover sheds light on the effect of pain treatment on sleep in people with dementia and depression, which can lay the ground for further investigation.

Sammendrag på norsk

Søvnforstyrrelser, smerte og depresjon er utbredt blant sykehjemspasienter og representerer en stor utfordring med hensyn til behandling. Denne avhandlingens formål var å undersøke kliniske evalueringsmetoder for søvn blant sykehjemspasienter, samt effektene av smertebehandling på søvn hos sykehjemspasienter med demens og depresjon. Avhandlingen er basert på to omfattende empiriske studier gjennomført ved norske sykehjem. I artikkel 1 gjennomførte vi en tverrsnittsstudie (n=83) hvor vi undersøkte i hvilken grad aktigrafibaserte og proxyrater-baserte evalueringer av søvn blant sykehjemspasienter gir sammenlignbare kliniske resultater. Vi sammenlignet søvnrelaterte mål i Cornell Scale for Depression in Dementia (CSDD) og Neuropsychiatric Inventory – Nursing Home version (NPI-NH) med søvnforstyrrelser identifisert med aktigrafi. I artikkel 2 og 3 gjennomførte vi en multisenter, toarmet, dobbelblindet, placebokontrollert, randomisert klinisk studie. De to siste artiklene i denne avhandlingen er basert på det sekundære formålet med studien, hvilket var å undersøke kortsiktige effekter (artikkel 2) og langsiktige effekter (artikkel 3) av smertebehandling på søvn målt med aktigrafi hos sykehjemspasienter med demens og depresjon (n=106).

I artikkel 1 fant vi at målinger med CSDD og NPI-NH hadde fra svært liten til liten sannsynlighet for å fange opp søvnutfall som ble avdekket ved hjelp av aktigrafimålinger. Vi konkluderte at det er begrenset nytte av proxyratermåling av søvn, og at ytterligere forskning på den kliniske verdien av slike målinger er nødvendig. Resultatene fra artikkel 2 og 3 avdekket at aktiv smertebehandling forbedrer aktigrafimålt søvn sammenlignet med placebobehandling på kort sikt (artikkel 2). Imidlertid er disse resultatene ikke gyldige på lang sikt (artikkel 3). Fra baseline til uke 13 var det betydelig bortfall av pasienter som mottok aktiv smertebehandling grunnet ulike reaksjoner på den aktive behandlingen, hvilket indikerer at det er nødvendig med forskning med hensyn til hvilken smertebehandling som kan tolereres best i denne gruppen. De underliggende mekanismene for disse

resultatene er imidlertid ukjente og fremtidig forskning bør undersøke dette ytterligere, da med annet design og med preparater som tåles bedre i denne pasientgruppen. Fremtidige studier bør også fokusere på den kliniske verdien av denne typen behandling. Oppsummert bidrar avhandlingen med ny innsikt i svakhetene knyttet til mulige evalueringsverktøy for søvn blant sykehjemspasienter. Videre belyser den effekten av smertebehandling på søvn, hvilket kan danne grunnlag for ytterligere forskning.

List of publications included in the thesis

Paper 1:

Blytt KM, Bjorvatn B, Husebo BS, Flo E. Clinically significant discrepancies between sleep problems assessed by standard clinical tools and actigraphy. *BMC Geriatrics*. 2017; 17(1), 253.

Paper 2:

Blytt KM, Bjorvatn B, Husebo BS, Flo E. Effects of Pain Treatment on Sleep in Nursing Home Patients with Dementia and Depression – A Multicenter Placebo-Controlled Randomised Clinical Trial. *International Journal of Geriatric Psychiatry*. 2018; 33(4), 663-670.

Paper 3:

Blytt KM, Husebo BS, Flo E, Bjorvatn B. Long-term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-week Randomized Placebo-Controlled Trial. *Frontiers in Psychology*. 2018; 9, 134.

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List of abbreviations

AASM – American Academy of Sleep Medicine
BPSD – Behavioural and Psychological Symptoms of Dementia
CSDD – Cornell Scale for Depression in Dementia
COSMOS – COmmunication, Systematic pain treatment, Medication review, Organized activities and Safety
DEP.PAIN.DEM – Efficacy of Pain Treatment on Depression in People with Dementia
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, fifth edition
DTS – Daytime Total Sleep Time
EEG – Electroencephalography
EOG – Electrooculogram
EMA – Early Morning Awakening
EMG – Electromyogram
ICD-10 – International Classification of Diseases, version 10
ICC – Intraclass Correlation Coefficient
MeSH – Medical Subject Heading
MMSE – Mini Mental Status Examination
MOBID-2 – Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale
NH – Nursing Home
NoW – Number of Wake Bouts
NPI – Neuropsychiatric Inventory
NPI-NH – Neuropsychiatric Inventory – Nursing Home version
NPS – Neuropsychiatric symptoms
NREM – Non Rapid Eye Movement
NSAID – Non-steroidal Anti-Inflammatory Drugs
PRN – Pro Re Nata (drugs as needed)
PSG – Polysomnography

RCT – Randomised Controlled Trial

REM – Rapid Eye Movement

SDI – Sleep Disorder Inventory

SE – Sleep Efficiency

SLEEP.PAIN.DEM – Efficacy of Pain Treatment on Sleep in People with Dementia

SOL – Sleep Onset Latency

SWS – Slow Wave Sleep

TST – Total Sleep Time

WASO – Wake after Sleep Onset

WHO – World Health Organization

1. Introduction

In recent decades, life expectancy has increased and the proportion of the population in need of nursing home (NH) services has consequently escalated (Statistics Norway 2018). NH patients are subject to multimorbidity and belong to a very fragile group. Sleep disturbances, dementia, pain and depression are all common in NH patients, and the combination of these often-coinciding conditions represents a comprehensive challenge for NH care (Flo et al. 2014).

Sleep is essential for good health and well-being, and sleep architecture changes from younger to older age. Sleep disturbances are common in people with dementia (McCleery 2014). Depending on the definition of sleep disturbances, study designs and sample populations, the prevalence of sleep disturbances varies from 25% to more than 60% (Neikrug et al. 2010; Ownby et al. 2014; Monane et al. 1996). Due to reduced ability to give valid self-report among people with dementia, however, identifying sleep disturbances in this population is methodologically challenging.

The causes of sleep disturbances may also be complex, and pain has been suggested as one underlying factor contributing to such disturbances (Flo et al. 2014). The presence of pain is widespread among elderly patients in NHs, and the causes of pain are similarly manifold (Achterberg et al. 2010). Furthermore, approximately 40-50% of patients with dementia experience symptoms of depression (Garre-Olmo et al. 2003). Previous research indicates that depression and pain share common signal pathways and neurotransmitters and are responsive to comparable treatment – a relationship often referred to as the pain-depression dyad (Buysse et al. 1991; Chopra et al. 2014). Studies conducted in people without dementia suggest that depression may act as a mechanism through which pain influences sleep (Nicassio et al. 2012; Valrie et al. 2007; Ravyts et al. 2018).

Two challenges in NH medicine serve as point of departure for this thesis. First, attaining valid information about subjective experiences in people with dementia or possible dementia may be difficult due to reduced communicative skills (Flo et al. 2014; Husebo et al. 2014a). In order to render such assessment possible for both research and clinical purposes, several clinical assessment tools for measuring sleep have been developed. It is, however, unclear to what extent they are used in the clinical setting. Being able to assess sleep using clinical assessment tools in NHs can be very valuable, and empirical investigation that can provide insight into the usefulness of such tools is therefore desirable. The first challenge thus relates to sleep assessment.

The second challenge relates to treatment that can improve sleep. Prior research has suggested that pain might be an important cause of sleep disturbances in NH patients with possible dementia (Flo et al. 2017; Chen et al. 2011), and that pain treatment could potentially improve sleep (Husebo et al. 2014b). However, this has not yet been investigated in a placebo-controlled trial. Furthermore, in the NH setting, treatment is often conducted by trial-and-error with different approaches. This leads to a process in which NH staff is continuously evaluating and redirecting when the desired result stalls. This may result in NH staff giving pain treatment to patients with symptoms of depression and disturbed sleep in the hope that this will reduce these symptoms. A recent publication shows that from 2000 to 2011, there was an increase from 1.9% to 17.9% of the prescription of strong opioids like fentanyl, buprenorphine, morphine and oxycodone in NH patients (Sandvik et al. 2016). The effect of these medications is, however, unclear. Thus, insight into the effect of pain treatment on sleep in NH patients with dementia and depression is of high clinical and scientific importance from the point of view of sleep medicine as well as geriatric medicine.

In this thesis, then, I aim to investigate possible clinical assessment methods of sleep in NH patients, as well as the effects of pain treatment on sleep in this patient group. By means of two large-scale studies carried out in Norwegian NHs, we conducted

three empirical inquiries. First, we investigated different methods for measuring sleep in NHs, and specifically the degree to which proxy-rater based assessments and the more objective measurement of actigraphy provided comparable results. The second and third inquiries were investigations of i) short-term and ii) long-term effects of pain treatment on sleep in NH patients with comorbid depression and dementia, by means of a large-scale randomised placebo-controlled clinical trial (RCT).

The remainder of the thesis is structured as follows. First, I outline the background of the study and review existing research. Second, I present the aims of the thesis. Third, I outline the methods employed in the three papers comprised in the thesis. Fourth, I present the results of the three papers. Fifth, I discuss the methods and findings of the three papers in light of the overarching aims of the thesis. Finally, I outline conclusions and discuss implications for clinical practice and for future research.

2. Background

In this chapter, I present the background, theory and prior empirical findings of relevance to the present inquiry. First, I outline the research setting by accounting for central characteristics of NH care and the nature and characteristics of patients with dementia. Second, I describe the nature of sleep, as well as the specific characteristics of sleep in the ageing population and among patients with dementia. I also account for assessment of sleep in this patient group. Third, I shed light on the nature of depression in general and of depression in patients with dementia in particular. Fourth, I account for pain in general and pain in NH patients in particular. Finally, I outline the rationale of the thesis.

The literature search upon which this chapter builds involved the following medical subject headings (MeSH) keywords: sleep and dementia; pain and dementia; depression and dementia, and a combination of these. The search was conducted in PubMed. While the rationale for the studies reported herein was established based on existing literature at the time I commenced this work, the three papers and the following chapters have also been informed by more recently published works. The most recent literature search was conducted in February 2019.

2.1 Research setting: Nursing home care and patients with dementia

As people above the age of 65 constitute a large and increasing proportion of the population, the demand for nursing and care services increases. As of the end of 2017, there were 32 733 long-term patients living in such institutions in Norway. In Norway, 1% of care service recipients are below the age of 50, while 74% are 80 years or older (Statistics Norway 2018). As many as 27 647 of the 32 733 long-term patients living in institutions have comprehensive assistance needs (Statistics Norway 2018).

Patients in NHs are commonly multimorbid and fragile (Fortin et al. 2005). Multimorbidity is defined by Boyd et al. (2010, p. 453) as “the co-existence of two or more chronic conditions, where one is not necessarily more central than the other”. The interaction of these diseases, the related drug treatment thereof, institutionalisation and loss of autonomy place NH patients in a very vulnerable position. In NHs, approximately 50% of patients have two to five diagnoses and approximately 30% have six or more diagnoses (Statistics Norway 2018). Furthermore, a diagnosis does not necessarily represent a chronic condition, but can be transitory. Previous research suggests that multimorbidity is associated with decreased function and quality of life, as well as with increased healthcare utilisation (Fortin et al. 2006; 2004; Bayliss et al. 2004).

2.1.1 Dementia

Dementia is a devastating chronic syndrome of cognitive decline, which is usually due to one or more neurodegenerative conditions that emerge in old age (Prince et al. 2016). It is an incurable and progressive disease and it leads to a decline in the individual’s cognitive and physical functions. The influence on brain function interferes with the individual’s ability to function at work, in everyday activities and in relationships (Prince et al. 2015; Alzheimer’s Disease International 2016). The individual’s cognitive functions typically deteriorate progressively. These include memory, attention, problem thinking, learning and the ability to orientate in new and old environments (Prince et al. 2015; Alzheimer’s Disease International 2016). As the disease progresses, it influences the individual’s language and ability to speak. Moreover, the individual may experience manifold challenges related to bodily changes, e.g. incontinence, muscle stiffness and balance problems (Edjolo et al. 2014).

Currently, approximately 46.8 million people worldwide suffer from dementia. Estimates suggest that the number will reach 131.5 million by 2050 (Prince et al.

2016). In NHs, 50-80% of patients have possible dementia (Helvik et al. 2015). The World Health Organization declared dementia a public priority, citing high global prevalence and economic impact on families, communities and health service providers (WHO 2016). Dementia is considered the most expensive of contemporary diseases, and it is minimally responsive to medication currently available (Thies et al. 2012).

Normally, a diagnosis of dementia is based on the criteria listed in the International Classification of Diseases, version 10 (ICD-10) (WHO 2015) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association 2013). It is worth noting that according to Statistics Norway (2018), only 16% of long-term patients living under institutional care are diagnosed with dementia. Studies investigating cognitive function through assessment scales suggest that approximately 50-80% of patients have dementia (Helvik et al. 2015; Røen et al. 2017). This is a challenge, since the planning of health and social care services and treatment relies on diagnostic coverage (Prince et al. 2016).

Neuropsychiatric symptoms (NPS) or behavioural and psychological symptoms of dementia (BPSD) represent central aspects of the condition (Selbæk et al. 2014). Such symptoms include hallucinations, delusions, depression, apathy, anxiety, aggression, agitation, aberrant motor activity, changes in appetite and sleep disturbances (Selbæk et al. 2014). NPS occur in more than 80% of people with any type of dementia (Lyketsos et al. 2002), and are perceived as very troublesome. One of these symptoms – sleep disturbances – is often the leading cause for NH admission (Luppa et al. 2008). The type of dementia and progression thereof will affect the prevalence and severity of the NPS (Bergh et al. 2011).

2.1.2 Different types of dementia

Since Alois Alzheimer published his historical thesis in the early 20th century, there has been knowledge on the histopathological signature of Alzheimer's disease – the amyloid plaques (Alzheimer, 1907). There are several subtypes of dementia, of which the most frequent are Alzheimer's disease, vascular dementia, and the related conditions of dementia with Lewy bodies and dementia in Parkinson's disease (McCleery et al. 2014). Alzheimer's disease accounts for approximately 70% of all dementia cases (Ott et al. 1995). Although its pathogenesis is still somewhat unclear, Alzheimer's disease is characterized by neurochemical and neuropathological changes. Its defining features are accumulation of amyloid- β peptides into extracellular plaques and development of intracellular neurofibrillary tangles due to hyperphosphorylation and accumulation of the tau protein (Rizzi et al. 2014). Other important features include visible changes in brain histology and behaviour.

Vascular dementia, the second most common form, represents approximately 20-25% of cases (Kalaria et al. 2008; Desmond 1996; Prince et al. 2016). Vascular dementia is a result of neuronal damage caused by a disruption in the blood vessels to the brain. This leads to different clinical presentations depending on which brain area is affected, severity and type of disruption (haemorrhagic or ischemic) (Khan et al. 2016). When comparing the clinical courses of Alzheimer's disease and vascular dementia, the development of the latter is more stepwise. Also, it is caused by distinct ischemic episodes (Dickson 2001). However, comorbid Alzheimer's disease and vascular dementia (so-called mixed dementia) is the most common form in NH patients (Scherder et al. 2003).

2.2 Sleep

Sleep is essential for good health and well-being, and every human being needs it. Sleep can be defined as “a reversible behavioural state of perceptual disengagement

from and unresponsiveness to the environment” (Kryger et al. 2017).

Polysomnography (PSG) gives comprehensive information about both sleep (classification of the different sleep stages) and wakefulness (Kryger et al. 2017; Sateia et al. 2000). PSG involves measurement of brain activity (electroencephalography [EEG]), eye movement (electrooculogram [EOG]) and muscle tone (electromyogram [EMG]). Clinical PSG often also involves assessment of respiratory, limb movement and cardiac activity (Kryger et al 2017). Based on PSG, we can broadly distinguish between rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. As defined by the American Academy of Sleep Medicine (AASM), NREM sleep comprises three stages: N1, N2, and N3 (Iber et al. 2007).

The change from wakefulness to stage N1 is defined as change from alpha waves (8-13 Hz – typically 9-11 Hz in adults) to theta waves (4-7 Hz). In stage N1, one may also observe vertex sharp waves and slow eye movements, but these are not required to score sleep as N1. In addition, reduced muscle tone and reduced awareness of the surroundings also characterise N1. Stage N2 is characterised by theta waves interspersed with specific EEG features, e.g. K-complexes and/or sleep spindles. In addition, further reduction in muscle tone and awareness is observed (Iber et al. 2007). N3 is also referred to as slow wave sleep (SWS) or delta sleep (deep sleep). It is characterised by waves with high amplitude (at least 75 μ V from peak-to-peak) and low frequency (< 2 Hz) that occupy at least 20% of the epoch (Iber et al. 2007). REM sleep is defined by EEG activation, similar but not identical to wakefulness and is not divided into stages. Furthermore, muscle tone is very low or absent in REM sleep (Kryger et al. 2017). The different sleep stages progress from NREM to REM, in a sleep cycle that lasts approximately 90 minutes. There are 4-5 cycles in one nocturnal sleep period. The majority of deep sleep and restorative NREM sleep takes place in the beginning of the sleep period, while REM sleep is more common in the last part (Kryger et al. 2017).

Individuals differ with regard to how much sleep they need to maintain a normal level of functioning and well-being (Bjorvatn and Pallesen 2009). Many bodily functions, like body temperature, degree of activation and secretion of hormones, follow a circadian rhythm. Circadian rhythms are 24-hour physiological rhythms regulated by an internal pacemaker in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus (Kryger et al. 2017). Light is the primary environmental rhythm modulator of the light-dark cycle (Kryger et al. 2017). The circadian phototransduction involves rods and intrinsically photosensitive retinal ganglion cells. In this process, retina converts light signals into neural signals for the SCN (Figueiro et al. 2017). During night and in darkness, the hormone melatonin is produced by the pineal gland and it signals when it is time to sleep (Figueiro et al. 2017). Melatonin production follows a cycle and the timing of melatonin onset in the evening is used as a marker for the circadian clock. This marker is referred to as dim light melatonin onset (Figueiro et al. 2017). Exposure to light at different times will affect the circadian rhythm system differently. Body temperature is often used as an expression for circadian rhythm and its lowest point reflects the rhythm base. This point is commonly known as nadir. Light in the morning, after nadir, which typically occurs approximately two hours before a person normally wakes up without alarm, will advance the timing of sleep. Light in the evening, before nadir, will delay the timing of sleep (Figueiro et al. 2017; Kryger et al. 2017).

The homeostatic process involves an accruing need for sleep as a result of the prior period of wakefulness (Borbély 1982). This implies that the need for sleep increases the longer a person stays awake, which is believed to have implications for sleep quality (Bjorvatn and Pallesen 2009). The homeostatic and the circadian timing system are results of complex interactions between several brain regions, neurotransmitter systems and modulatory hormones (Wulff et al. 2010). Together with behavioural, environmental, individual and social processes, they regulate the quality, timing and duration of sleep (Bjorvatn and Pallesen 2009). In summary, achieving high sleep quality requires staying awake for a substantial amount of time,

and getting stable sleep duration requires regular bed and rise times (Bjorvatn and Pallesen 2009).

2.2.1 Sleep and ageing

Approximately 40% to 70% of older adults suffer from sleep disturbances (Van Someren et al. 2000; Maggi et al. 1998). With increasing age, sleep becomes more fragmented (Bliwise et al. 2009) and there is a decline in SWS and REM sleep (Ohayon et al. 2004). Older people spend more sleep time in the lighter stages of sleep (N1 and N2), which in turn increases the possibility for waking up more often during the night (Ancoli-Israel and Cooke 2005). Despite this, previous research suggests that older adults sleep approximately seven hours at night, which is comparable to younger adults (Ancoli-Israel 2009).

Insomnia is one of the most widespread sleep disorders among adults (Mai et al. 2008; Ancoli-Israel and Cooke, 2005). The definition of insomnia is subjective poor sleep attributed to problems with sleep onset, troubled night-time sleep or too early morning awakening (Manjavong et al. 2016; Kryger et al. 2017). In the adult population, prevalence studies suggest that approximately 10-20% suffer from insomnia (Ohayon et al. 1997; Pallesen et al. 2001). Among the elderly, however, reported prevalence of insomnia ranges from 45% to 60% (Manjavong et al. 2016; Kryger et al. 2017). The condition is associated with feeling unrefreshed, daytime sleepiness, impaired daytime attention and depression (Kryger et al. 2017).

As age advances, the circadian rhythms may become weaker and less synchronised (Dijk et al. 1995; Ancoli-Israel and Cooke 2005; Forbes et al. 2014). A shift in older adults' sleep/wake cycle is also often observed. This condition is denoted advanced sleep phase syndrome (Campbell et al. 1995). In elderly patients, this syndrome may lead to sleepiness early in the evening and early morning awakening. It may result in patients waking up at night and not being able to go back to sleep (Ancoli-Israel and

Cooke 2005). Several other sleep disorders are common in older adults, including periodic limb movements in sleep, sleep-disordered breathing, restless legs syndrome and REM sleep behaviour disorder (Ancoli-Israel and Cooke 2005).

2.2.2 Sleep in people with dementia

As previously mentioned, identifying sleep disturbances often depends on self-report, which can make it difficult to identify and treat such disturbances in people with dementia. Different studies report varying prevalence depending on how sleep disturbances are defined and which measurements are used. Studies report that approximately 60% of NH patients experience sleep disturbances, and prevalence differs according to the type of dementia (Neikrug and Ancoli-Israel 2010; Ownby et al. 2014). Sleep disturbances are reported in 25-35% of people with Alzheimer's disease (Dauvillers 2007). The prevalence of sleep disturbances in people with vascular dementia is similar to that of Alzheimer's disease. However, Fuh et al. (2005) found higher prevalence of sleep problems among patients with cortical vascular dementia. Sleep disturbances are particularly prevalent in people with Lewy bodies and Parkinson's disease dementia. Compared to people with Alzheimer's disease, these patients have higher rates of insomnia, excessive sleepiness, dyssomnias and parasomnias (Bliwise et al. 2011; Rongve et al. 2010). While studies have identified a link between neurodegeneration and sleep disturbances, the mechanisms are not fully understood. Research suggests that β -amyloid ($A\beta$) accumulation affects sleep, though this is probably mediated by several other variables (Holth et al. 2017). This was supported by the study by Fjell et al. (2018), which investigated to what extent biomarkers could predict sleep over a 3-year period in β -amyloid positive individuals. Fjell and colleagues found that multiple variables predicted sleep outcomes, including higher levels of tau and YKL-40 in the cerebrospinal fluid, depression scores, more brain atrophy and lower memory function (Fjell et al. 2018).

Sleep disturbances can be quite severe for people with dementia, and some of them may experience less than an hour of undisturbed sleep at any time (Bliwise et al. 1989). The most common sleep disturbances are increased sleep onset latency, fragmented sleep at night, early morning awakening, and excessive daytime sleepiness (McCleery et al. 2014). These are all examples of abnormalities in sleep regulation. In people with dementia, low amplitude of the circadian rhythm may lead to mistimed and poorly consolidated bouts of sleep and wakefulness. Sleep disturbances in this group may thus be a direct result of neurodegeneration in the sleep-wake circuitry (McCleery et al. 2014). When compared to the younger population, people aged 65 and older are at risk of experiencing changes in the core body temperature, melatonin rhythm and circadian rest-activity cycle. These changes may manifest as fragmented nocturnal sleep, multiple and prolonged awakenings and more daytime napping (Forbes et al. 2014). Furthermore, these changes are more prevalent in people with dementia (McCurry et al. 2000).

In addition to circadian rhythm disturbances, several other factors may contribute to sleep disturbances in people with dementia. The causes of sleep disturbances are comparable to those in people without dementia. The causes include pain (Flo et al. 2017; Chen et al. 2011), physical health conditions, polypharmacy (Jokanovic et al. 2015) and depression (Giron et al. 2002; Ownby et al. 2014). Being under institutional care might also contribute to sleep problems. For instance, artificial light exposure at night due to lights from bathrooms or corridors can shift the timing of the circadian pacemaker (Forbes et al. 2014). Noise from staff or other patients may also influence the patient's ability to sleep. Daytime light exposure is rare among NH patients, which may also contribute to sleep difficulties at night (Forbes et al. 2014).

Furthermore, sleep disturbances in people with dementia may be due to neurodegeneration in the suprachiasmatic nucleus or impaired melatonin production and release (Kinnunen et al. 2017; Van Someren 2000; Swaab et al. 1985; Gubin et al. 2016). Changes observed in relation to normal ageing are exaggerated in long-

term care patients (Neikrug and Ancoli-Israel 2010). Moreover, research has documented changes in the sleep architecture of people with Alzheimer's disease, including a reduction of slow wave sleep (SWS), sleep spindle activity and REM sleep (Montplaisir et al. 1995; 1998). There is, however, no evidence suggesting that these changes are associated with subjective sleep disturbances.

Sleep disturbances in people with dementia have manifold and potentially severe consequences. In institutionalised patients, sleep disturbances may impair daytime function (Cricco et al. 2001), reduce quality of life, and reduce memory and concentration (Ancoli-Israel and Cooke 2005). Sleep disturbances in NH patients may also have other consequences such as increased risk of falls, hip fractures (Stone et al. 2004; Widera 2013), and decreased survival (Dew et al. 2003). Sleep disturbances in people with dementia may moreover affect the sleep of those living at home with a carer (McCurry et al. 2007). Previous research shows that sleep disturbances may result in increased caregiver distress, which in turn increases the possibility that patients become institutionalised (Donaldson et al. 1998; Gaugler 2000). Improving the treatment of sleep disturbances in NH patients would not only benefit the condition for patients, but also reduce the strain on NH staff (Pollak and Perlick 1991).

2.2.3 Assessing sleep disturbances in people with dementia

In light of the potentially severe consequences of sleep disturbances for NH patients, detection and treatment should have high clinical priority. However, the assessment and identification of sleep disturbances in people with dementia can be challenging. Several methods are used to assess sleep, of which I will emphasise three: PSG, actigraphy and proxy-rater assessment of sleep.

PSG was introduced in the 1950s, and has since been regarded as the gold standard for measuring sleep. PSG is, however, not a feasible method for measuring sleep in

people with dementia for the following reasons: 1) some patients with dementia might perceive it as overly invasive; 2) electroencephalography does not produce clear patterns of sleep stages in people with dementia, and PSG results for patients with dementia are consequently very difficult to score (Bliwise 1993; Ancoli-Israel et al. 1997).

Actigraphy records and generates 24-hour objective information on wakefulness and sleep based on activity/inactivity, and it is usually tolerated by patients with dementia (Kryger et al. 2017). Actigraphy equipment consists of an accelerometer and a memory storage unit, and is usually a watch-like device that patients can wear on the wrist. It is therefore considered to be a relatively non-invasive method for assessing sleep. Since PSG is the gold standard for sleep measurement, actigraphy measures should ideally correspond with PSG measurement. Sivertsen et al. (2006) found that actigraphy had high sensitivity (92.5%), but that its specificity (i.e. ability to detect wakefulness) was 36.3% among older adults treated for chronic insomnia. Sivertsen et al. (2006) therefore concluded that the clinical utility of actigraphy is still suboptimal, at least in older adults with insomnia. It is however noteworthy that Ancoli-Israel et al (2003) concluded that actigraphy is reliable for assessing sleep patterns in people with insomnia, evaluating sleep in people who are less likely to tolerate PSG (such as patients with dementia) and for studying the effects of treatment which intend to improve sleep, among others.

Sleep diaries are important clinical tools for subjective sleep assessment in the broader population (Carney et al. 2012), but their validity is questionable when used in people with dementia. Therefore, validated proxy-rated assessment tools could be useful to assess sleep in this patient group. Proxy-rater measurements can provide valuable information about patients based on the observations of close caregivers who function as proxy-raters. It is, however, essential that the proxy-rater has been familiar with the patient over time. This will provide the rater with knowledge about

the patient's behaviour and render the proxy-rater able to identify changes. However, few assessment tools are validated for measuring sleep in NH patients.

One assessment tool for measuring sleep is the Sleep Disorders Inventory (SDI), which is an expanded version of the sleep and night-time behaviour item in the Neuropsychiatric Inventory (NPI) (Cummings 1997). The SDI has been tested on people with Alzheimer's disease who are living at home with a caregiver (Tractenberg et al. 2003). The SDI is found to have good validity for patients living at home and has been recommended for use in sleep research (Tractenberg et al. 2003). Other instruments, like the Cornell Scale for Depression in Dementia (CSDD), which is developed to measure depression in people with dementia, also contains items which evaluates sleep (Alexopolous et al. 1988a; 1988b; Barca et al. 2010).

2.2.4 Treatment of sleep disturbances in people with dementia

Medications are often sought to alleviate sleep disturbances in people with dementia. There is, however, no conclusive evidence that medications are effective, and they can also have harmful side-effects (McCleery et al 2014; Rapaport et al. 2018). Since sleep disturbances in persons with dementia may originate from changes in the brain caused by dementia, it is not clear whether regular sleep medications are effective (McCleery et al. 2014; Kinnunen et al. 2017; Van Someren 2000). Furthermore, research suggests that treating sleep disturbances increases amyloid deposition, and it is therefore possible that treating sleep disturbances may slow the progression of dementia (Holth et al. 2017). Different sleep disturbances call for different types of treatment, and there is need for more research that differentiates between types of sleep disturbances in this patient group and the treatment thereof.

Several studies have examined how bright light therapy may affect sleep in people with dementia (Fetveit et al. 2004; Skjerve et al. 2004; Forbes et al. 2014). However, a recent Cochrane review found no effective treatment for sleep disorders in this

patient group (Forbes et al. 2014). Meanwhile, a more recent meta-analysis investigating the effect of bright light on sleep problems found a positive effect on sleep problems (van Maanen et al. 2016). Chiu et al. (2017) found that light therapy had a positive effect on behavioural disturbances, total sleep time and depression. A Cochrane review investigating the effect of different pharmacotherapies found no indication of improvements for ramelteon (selective melatonin receptor agonist for treatment of insomnia [Neubauer et al. 2008]) and melatonin. However, the use of 50 mg Trazodone (triazolopyridine antidepressant used for treatment of insomnia [Mendelson, 2005]) showed increased nocturnal sleep time and sleep efficiency in patients with Alzheimer's disease (McCleery et al. 2014).

The difficulty of detecting and treating sleep disturbances in people with dementia suggests a need to investigate methods and treatments that can potentially improve the lives of these patients. As highlighted by Kinnunen et al. (2017), sleep is one of the cornerstones of human well-being. There is a pressing need for treatments that work and that can be used over the longer time periods. In light of this, clinical trials investigating potential treatments are highly needed.

2.3 Depression

According to DSM-5 criteria for major depressive disorder, the following symptoms have to be present during the same two-week period and represent a change from previous functioning: 1) depressed mood or 2) loss of interest or pleasure (American Psychiatric Association 2013). Symptoms include loss of appetite, energy, reduced concentration, sleep disturbances and pronounced fatigue. Changes in sleep profile are reported among 90% of the people experiencing an acute depressive episode (Wulff et al. 2010). Worldwide, approximately 300 million people of all ages suffer from depression (WHO 2017).

2.3.1 Depression in people with dementia

In people with dementia, the occurrence of depressive symptoms is found to be approximately 40-50% (Garre-Olmo et al. 2003). Depression occurs more often in people with vascular dementia and dementia with Lewy bodies, compared to people with Alzheimer's disease (Ballard et al. 2000; Borroni et al. 2008). In people with dementia, depression is often persistent or follows a fluctuating course (Borza et al. 2014). With increasing dementia severity, depression is more prevalent, which in turn causes increased suffering and reduced quality of life (Gonzalez-Salvador et al. 2000). Furthermore, some studies indicate that people with dementia and depression may be at risk of worse outcomes after undergoing medical treatment, and have increased mortality compared to those without depression (Bellelli et al. 2008; Rapp et al. 2011).

2.3.2 Assessment of depression in people with dementia

Diagnosing depression in people with dementia is difficult because of an overlap between the symptoms of depression and the early stages of dementia (Enache et al. 2011). The symptoms observed in the early stages of dementia progression, such as reduced memory or lack of initiative, are also symptoms of depression (Brailean et al. 2016). The above-mentioned CSDD is a reliable and valid assessment tool for measuring depression in this population. The CSDD consists of 19 items measuring five different domains related to depression. These domains are mood, behavioural disturbances, physical signs, cyclic functions and ideational disturbance (Alexopolous et al. 1988a; 1988b; Barca et al. 2010). The CSDD is often administered using proxy-raters who are familiar with the patient. Jeon et al. (2015) compared and analysed CSDD scores from proxy-raters against expert diagnoses by means of ROC curves. They concluded that the clinical utility of the CSDD is questionable. In contrast, Hancock et al (2015) concluded that the CSDD was useful as a brief screening test for patients in a memory clinic.

2.3.3 Treatment of depression in people with dementia

In 2017, the Norwegian Directorate of Health published guidelines for the treatment of depression in people with dementia (Norwegian Directorate of Health 2017). These recommendations correspond with other national guidelines. As first-line treatment, non-pharmacological treatment is recommended. This includes psychological treatment, person-centred care and reminiscence therapy. Studies investigating these interventions give some support that they reduce depressive symptoms in people with dementia and depression (Kales et al. 2015; Testad et al. 2014; Orgeta et al. 2015). When non-pharmacological treatment has been attempted and no effect is seen, or depressive symptoms persist, pharmacological treatment is recommended. However, the decision to start treatment should be based on an evaluation of patients' comorbidity, preferences and polypharmacy. It should also involve a careful evaluation of risk versus potential benefits. However, systematic reviews and meta-analyses investigating the efficacy of antidepressants for depression in people with dementia conclude that there is little support to recommend this treatment (Bains et al. 2002; Nelson et al. 2011; Leong et al. 2014). A study conducted by Banerjee et al. (2011) included 326 patients with depression and dementia. In this study, patients were allocated to receive mirtazapine, sertraline or placebo for 39 weeks with follow-up at week 13 and 39. In all three groups, CSDD scores had improved significantly in week 13, and this was unchanged from week 13 to the follow-up at week 39. Taken together, studies investigating the efficacy of antidepressants highlight that there is no robust evidence to support treatment with antidepressants in this patient group. In light of these studies, investigating other potentially beneficial treatments are highly needed.

2.4 Pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential

tissue damage, or described in terms of such damage” (IASP 2017). Thus, it is a subjective experience. It is common to classify pain into two main types: nociceptive and neuropathic pain. According to the IASP, nociceptive pain denotes “pain that arises from actual or threatened damage to non-neural tissue and is due to activation of nociceptors”. Nociceptive pain includes somatic pain (pain derived from the musculoskeletal system) and visceral pain (pain related to the internal organs) (IASP 2017). Neuropathic pain is related to the nervous system and is a result of a lesion or disease of the somatosensory system (IASP 2017; Dworkin 2012).

2.4.1 Pain in people with dementia

Pain is very common in people with dementia, and 40-60% of NH patients are estimated to experience daily pain (Achterberg et al. 2010). Pain may remain undetected, since people with dementia experience reduced ability to communicate and evaluate pain symptoms (Flo et al. 2014). Because pain is difficult to assess and recognise in people with dementia, pain is acknowledged as a major clinical challenge in this patient group. Therefore, it is important that a caregiver who is familiar with the patient observes the patient and is aided by validated assessment tools in the attempt to identify pain. The consequences of untreated pain may be manifold. Pain is associated with reduced quality of life, decline of activities of daily living, physical and mobility disability (Flo et al. 2014).

2.4.2 Assessment of pain in people with dementia

Several assessment tools have been developed for measuring pain in people with dementia, and such tools are designed to capture potential changes in patients’ typical behaviour when experiencing pain (Corbett et al. 2012; Sandvik 2017). Although pain is a subjective experience, in the NH setting, pain is often assessed by a proxy or a stand-in for the patient. In many cases, this is the patient’s primary nurse or another health care professional familiar with the patient. As pointed out by

Hadjistavropoulos et al. (2010), however, the best clinical practice for pain assessment is to use the patient's own self-reported data, when such information is possible to provide. The guidelines of the American Geriatric Society (AGS) Panel on Persistent Pain in Older Persons recommends evaluation of facial expressions, verbalisation and vocalisations, body movements, changes in interpersonal interactions, changes in activity patterns or routines and/or mental change (AGS 2002). When NH patients experience persistent pain, functional and mental capacities may decline (Husebo et al. 2012). Manifest outcomes are associated with pain in NH patients, including reduced quality of life (Cordner et al. 2010), increased agitation (Husebo et al. 2011), depression and anxiety (Snow 2006).

2.4.3 Pain treatment in people with dementia

A systematic review shows that when comparing people with and without dementia, people with dementia receive fewer analgesics (Tan et al. 2015). However, more recent research indicates that this discrepancy is decreasing and that there has been an overall increase in the use of opioid analgesics (Sandvik et al. 2016; Tan et al. 2016). The most used non-opioid analgesic in NH patients with dementia is paracetamol. Sandvik et al. (2016) found that 48% of patients were prescribed paracetamol in 2011, which had increased from 23% in 2003. A central question is whether the treatment is effective. A double-blind, placebo-controlled crossover study investigating pain treatment (acetaminophen [paracetamol] 650 mg four times a day versus as-needed administration of acetaminophen) found no significant differences in discomfort scores between the different trial arms (Buffum et al. 2004). Chibnall et al. (2005) investigated the effect of acetaminophen on behaviour, well-being, and psychotropic medication use in NH patients with moderate to severe dementia. They concluded that NH patients who received active pain treatment spent more time in social interaction and work-like activity. The authors therefore concluded that untreated pain inhibits activity in NH patients. Erdal et al. (2018) found no significant reduction in pain in the group of patients receiving active pain

treatment (paracetamol and buprenorphine combined) compared to placebo. However, when conducting sub-group analyses, Erdal et al. (2018a) found a significant reduction in pain for those patients who received active paracetamol versus placebo. Taken together, the inconsistency of these results suggests that more research is necessary to investigate this relationship further.

2.5 The rationale of the studies in the thesis

Paper 1

To the best of my knowledge there are no studies investigating the degree to which proxy-rater assessment tools identify sleep disturbances, as compared to actigraphy assessment, in the NH setting. The NPI-NH contains a sleep-related item that can be used to assess sleep. In addition, the CSDD, which is developed and validated to evaluate depression in this patient group, contains several items regarding sleep. It is likely that these items provide some information regarding how the NH staff considers the patients' sleep.

Towards this backdrop, the first rationale of this thesis was as follows:

- 1) Identifying and treating sleep disturbances in NH patients should be a clinical priority.
- 2) Few studies have investigated the sleep of NH patients as measured with proxy-rater assessment tools and actigraphy.
- 3) It is valuable to compare the different methods in order to assess their strengths and weaknesses. This could provide new knowledge regarding the assessment of sleep in this patient group.

Papers 2 and 3

Research on the previously mentioned pain-depression dyad suggests that pain and depression often coexist and exacerbate each other (Goldenberg et al. 2010; Bair et al. 2003). Moreover, pain and depression share joint signal pathways and neurotransmitters, and respond to comparable treatments (Chopra et al. 2014; Buysse et al. 1991). In previous research on neuropsychiatric symptoms, sleep is found to cluster with depression, anxiety and eating and appetite disturbances (Aalten et al. 2003; Hollingwoth et al. 2006; Cheng et al. 2012; Selbaek et al. 2012), which gives support for the link between sleep and depression. Pain may lead to depression, which in turn may influence the patient's sleep (Flo et al. 2017; Niacassio et al. 2012; Valrie et al. 2008). Among patients with depression, as many as 90% have sleep complaints like frequent awakenings during the night, early morning awakenings and/or difficulties initiating sleep (Hamilton et al. 1989; Perlis et al. 1997; Franzen et al. 2008). Senba (2015) points out that chronic pain often coexists with insomnia, and that sleep and pain symptoms are considered to be reciprocally interacting (Senba 2015; Finan et al. 2013; Lautenbacher et al. 2005). Smith et al (2005) found that approximately 50% of the patients with insomnia suffer from chronic pain (Smith et al. 2004). In clinical cases, it is well known that insomnia exacerbates pain and experimental studies have shown that sleep deprivation increases pain sensitivity (Finan et al. 2013; Sivertsen et al. 2015). People with dementia and depression may be lying in bed, experiencing difficulty falling asleep or maintaining sleep because they are in pain. At the same time, these patients have reduced capacity to express their symptoms due to dementia. In such cases, the patients may receive sleep medication, when they are in fact experiencing pain. Secondary analyses from a cluster-randomised controlled trial showed that pain management had beneficial effects on mood symptoms, depression, apathy and sleep in people with agitation and dementia (Husebo et al. 2014). However, this was not a placebo-controlled trial, and only participants with clinically significant agitation were included. Taken together, we see that there is growing support of the hypothesis that pain, depression and sleep

disturbances are linked and exacerbate each other, as visualized in Figure 1 below. Additionally, as shown by Husebø et al. (2014), giving pain treatment may improve sleep.

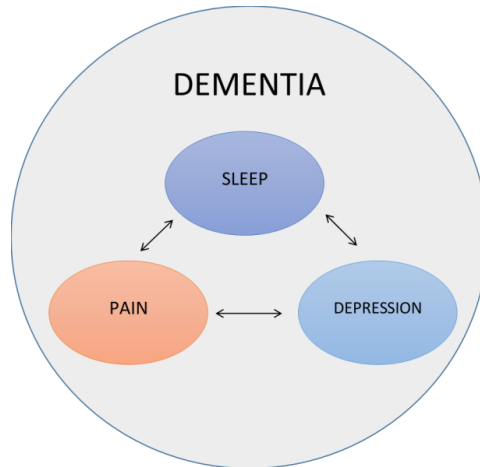


Figure 1: The relationship between pain, depression and sleep in patients with dementia (based on Senba 2015). Dementia is presented as an underlying factor influencing all of the variables.

Towards this backdrop, the second rationale of this thesis was as follows:

- 1) Depression, pain and sleep may interact and reciprocally influence each other. Specifically, pain may lead to sleep problems, either through a direct route or mediated by depression.
- 2) Giving pain treatment may therefore enhance sleep in people with dementia and depression.

3. Aims

The aim of this thesis was threefold. Its first aim was to investigate the degree to which actigraphy-based and proxy-rater-based assessments of sleep in NH patients provide comparable clinical outcomes. Its second and third aim was to investigate i) the short-term and ii) the long-term effects of pain treatment on sleep in people with comorbid dementia and depression. The thesis comprises three papers, which have the following aims:

Paper 1:

The first paper of the thesis is entitled *Clinically Significant Discrepancies between Sleep Problems Assessed by Standard Clinical Tools and Actigraphy*. It aimed to investigate different methods to assess sleep in NH patients. In addition, it aimed to investigate the degree to which actigraphy-based and standard proxy-rater-based assessments of sleep in NH patients provide similar results. The paper was published in *BMC Geriatrics* in 2017.

Paper 2:

The second paper of the thesis was entitled *Effects of Pain Treatment on Sleep in Nursing Home Patients with Dementia and Depression – A Multicenter Placebo-Controlled Randomised Clinical Trial*. It aimed to investigate the short-term effects of pain treatment on sleep in NH patients with dementia and depression in a placebo-controlled randomised clinical trial with objective sleep measurements. The paper was published in the *International Journal of Geriatric Psychiatry* in 2018.

Paper 3:

The third paper of the thesis was entitled *Long-term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-week Randomized Placebo-Controlled Trial*. It aimed to investigate the long-term effects of pain treatment on 24-hour sleep patterns in NH patients with dementia and

depression in a placebo-controlled randomised clinical trial with objective sleep measurements. The paper was published in *Frontiers in Psychology* in 2018.

4. Methods

In this chapter, I give an account of the research design and methodological choices of the studies. First, I give a brief introduction to the datasets on which the thesis builds. Second, I outline the assessment tools used in the thesis. Third, I discuss the methods used in paper 1. Fourth, I discuss the experimental design of the RCT upon which papers 2 and 3 build.

4.1 A brief introduction to the datasets

Prior to the presentation of the research design and methodological choices, I introduce the two empirical studies from which the datasets are derived. Paper 1 uses data from the COSMOS study (*COmmunication, Systematic pain treatment, Medication review, Organized activities and Safety*) (Husebo et al. 2019). The COSMOS trial was approved by the Regional Committee for Medical and Health Research Ethics West Norway (REK 2013/1765), and was registered at www.clinicaltrials.gov (NCT02238652). The COSMOS study is a four-month cluster-randomised trial with follow up at month nine. The primary outcome was quality of life in NH patients after a complex intervention. The study, which included 67 NH units, took place in Norway between January 2014 and December 2015. I was not involved in the COSMOS data collection process, and the secondary analyses of baseline data in paper 1 was not initially part of the COSMOS study design.

Papers 2 and 3 use data from the DEP/SLEEP.PAIN.DEM study – a multicenter, randomised, placebo-controlled trial. The Norwegian Medicines Agency (EudraCT 2013-002226-23) and the Regional Ethics Committee West (REC-West 2013/1474) granted approval to the DEP/SLEEP.PAIN.DEM study. The study's Clinical Trial number is NCT02267057.

The present thesis builds on the sleep data from this trial. The following assessment tools are used in the papers: actigraphy, the Mini Mental Status Examination (MMSE), the CSDD and the NPI-NH. I conducted the entire data collection for the RCT reported in papers 2 and 3 together with Ane Erdal, whose PhD thesis was based on the primary outcome (depression).

4.2 Assessment tools used in the thesis

In the following, I will describe the assessment tools used in the present thesis – actigraphy and various proxy-rater tools:

4.2.1 Actigraphy

We used the *Actiwatch Spectrum (Philips Respironics)* for actigraphy measurement and *Actiware 6 (Respironics)* for sleep scoring. We set the sensitivity setting to medium, and the sleep/waking status was determined by the actiware software for each one-minute epoch. A trained technician conducted the process of scoring the activity protocols. A standardised hierarchical approach was used in order to set rest intervals for the actigraphy data. The following approach was used: 1) event markers when possible; or 2) light and activity data; or 3) light or activity data. We only implemented alternatives 2 and 3 if there was a clear differentiation between active and rest periods. If not, we excluded the actigraphy protocol. This approach applies to all three papers.

4.2.2 Neuropsychiatric inventory – Nursing Home version

The NPI-NH evaluates 12 neuropsychiatric symptoms in people with dementia; respectively: delusions; hallucinations; agitation; dysphoria; anxiety; apathy; irritability; euphoria; disinhibition; aberrant motor behaviour; and night-time behaviour and appetite (Cummings 1997) (see Appendix 1). In the data collection

process of the COSMOS study, neuropsychiatric symptoms were assessed in an interview with the patient's primary caregiver using the NPI-NH. The NPI-NH produces an item score by multiplying the frequency and the severity of symptoms. Several studies have investigated the underlying factor structure of the NPI-NH and found the presence of three behavioural sub-syndromes: mood/apathy, psychosis, and hyperactivity. The sleep item was found to cluster with depression, anxiety and eating and appetite disturbances in the mood/apathy cluster (Aalten et al. 2003; Hollingworth et al. 2006; Cheng et al. 2012; Selbaek et al. 2012). The NPI-NH was used in paper 1 to assess sleep.

4.2.3 Cornell Scale for Depression in Dementia

The CSDD is validated to measure depression in people with dementia (see Appendix 2). When using the CSDD, the proxy-rater gives a score for each of the 19 items ranging from zero (no depression) to two (severe symptoms), or the letter "a", which implies that the symptom is not possible to evaluate. A total score is provided by adding all the results together. This provides a total score ranging from zero to 38 (which is consistent with very severe depression). Barca et al. (2015) investigated the factor structure of the CSDD among 1682 patients with mild to severe dementia and identified five clusters of symptoms: mood, physical, cyclic, retardation and behaviour. The cyclic factor included multiple awakening, difficulty falling asleep and early morning awakening. All factors except mood and cyclic factors were found to increase as dementia progresses (Barca et al. 2015). A recently conducted meta-analysis and systematic review found optimal sensitivity using a cut-off of equal or over 6 (sensitivity 0.91 and specificity 0.73), and optimal specificity using a cut-off of equal or over 8 (sensitivity 0.78 and specificity 0.84) (Goodarzi et al. 2017). The CSDD was used in paper 1 to investigate the correspondence between sleep items and actigraphy. In addition, the CSDD was used in the screening process of the DEP/SLEEP.PAIN.DEM to include participants.

4.2.4 Mini Mental Status Examination

The MMSE is a brief cognitive screening test with a 30-point scale that consists of 20 tasks (see Appendix 3), which gives indications of probable dementia (Creavin et al. 2016). The MMSE is administered in direct interview with the patient. When using the MMSE, there are several important limitations that need to be acknowledged. Daily fluctuations in mood, vision, hearing ability, hunger, sleepiness, comfort, pain, stress, the temperature in the room, and the cooperation with interviewer are all aspects that may influence the answers from the responder. In addition, educational level, age and gender may also influence the answers (Creavin et al. 2016; De Silva et al. 2008; Finney et al. 2016). Some of these aspects can be handled before the interview begins, such as room temperature or hunger. We used the MMSE to assess patients' cognitive function in all three papers. MMSE scores from 0 to 10 suggest severe dementia, 11 to 20 point to moderate dementia, 21 to 25 suggest mild dementia, and scores of 26 to 30 indicate no dementia (Perneckzy et al. 2006). It is important to highlight that the MMSE test can not be used alone to diagnose dementia (Creavin et al. 2016), and in the papers included in the present thesis we only use the MMSE results as an indication of probable dementia.

4.2.5 Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale

Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale (MOBID-2) is a validated, staff-administered instrument for measuring pain in people with advanced dementia (Husebo et al. 2007) (see Appendix 4). The score is based on the patient's pain behaviour in connection with standardised guided movements when the patient is lying in bed. In addition, it evaluates pain behaviour related to internal organs, head and skin (Husebo et al. 2007). A total score, ranging from 0 to 10, of which 10 represents the worst possible pain, is generated through an evaluation of all observations. The cut-off to indicate clinically relevant pain is a score of ≥ 3 (Husebo et al. 2007; 2014). The MOBID-2 was used to assess pain in papers 2 and 3.

4.3 Methodological choices in paper 1

4.3.1 Design

The study in paper 1 has a cross-sectional design. We conducted secondary analyses on baseline data from the COSMOS trial (Husebo et al. 2015; 2019). The COSMOS dataset is comprehensive, and we used its baseline data on patient characteristics, sleep outcomes as measured by actigraphy and scores from the various proxy-rater instruments. This enabled us to compare sleep assessments by the different measures for each of the patients included in the study.

4.3.2 Settings, participants and data collection

The COSMOS trial was conducted at Norwegian NHs, and 700 patients were invited to participate. A research team containing of five persons (two PhD candidates, two research assistants and a medical professor) performed the data collection in cooperation with NH staff and patients. The research team included eight different NHs in the study. The intervention lasted four months, with data collection conducted at baseline, and after four and nine months, respectively. The intervention consisted of a standardised educational program. In paper 1, we include data assessed at baseline – before any intervention occurred. The nurses who functioned as proxy-raters for the patients were instructed in the use of the different assessment scales prior to the evaluation.

From this study population, 545 participants from 67 NH units at the eight NHs were included. Both urban/rural and large/small municipalities were included in order to gain a representative distribution of NHs. Inclusion criteria are listed in the sub-section immediately below. After applying the inclusion criteria, we included 107 patients in the actigraphy sub-project for paper 1. However, 24 patients were in turn

excluded, either because of missing data or due to actigraph malfunction. Thus, the final sample included 83 patients, for whom actigraphy measurement was completed and CSDD and NPI-NH scores were collected.

4.3.3 Inclusion and exclusion criteria

The following inclusion criteria were applied for the COSMOS trial:

- NH patients who were ≥ 65 years old,
- with life expectancy > 6 months,
- who were not diagnosed with schizophrenia

The following patients were excluded from the actigraphy measurement:

- patients who had paralysis in the arms or upper body,
- or who had any form of chronic movement disorder
- or who were bed-ridden

4.3.4 Outcomes

In order to compare actigraphy-based and proxy-rater-based assessments of sleep, we had to define what constitutes disturbed sleep in this population. We applied the quantifiable criteria described in the DSM-5 diagnostic features for insomnia (American Psychiatric Association 2013). These cut-off points were used to define sleep disturbances as measured with actigraphy: sleep onset latency (SOL) > 30 minutes; wake after sleep onset (WASO) > 30 minutes; early morning awakening (EMA) > 30 minutes. In addition, we used a cut-off of number of wake bouts (NoW) ≥ 3 and a cut-off for sleep efficiency (SE) $< 85\%$ (Lacks and Morin 1992).

To provide proxy-rater-based assessments of sleep, we used the sleep-related items in the Neuropsychiatric Inventory – Nursing Home version (NPI-NH) and in the Cornell Scale for Depression in Dementia (CSDD). The sleep-related item in the NPI-NH is

item number 11 – night-time behaviour. It is important to note that the NPI-NH is the short version of the instrument. It is different from the more comprehensive version, which is named the NPI (see Appendix 1 for the NPI-NH).

When scoring the sleep-related item in the NPI-NH, proxy-raters were asked the following questions (reprinted from paper 1):

- Does the patient have sleep problems?
- Is s/he awake during the night?
- Does s/he wander during night-time, getting dressed, or going into the room of others?

We calculated a product score for each patient. It was based on the frequency score for each symptom (score 1–4) and the corresponding severity score (score 1–3). In line with previously conducted studies, we used a cut-off at product score ≥ 4 to define the presence of sleep disturbances (Garcia-Alberca et al. 2013; Chwiszczuk et al. 2016).

We used the CSDD to measure sleep as observed and judged by proxy-raters. In the category “cyclic functions”, the instrument includes the following three questions regarding sleep (reprinted from paper 1):

- Item 13: “Does the patient have difficulty falling asleep?”
- Item 14: “Does the patient have multiple awakenings during sleep?”
- Item 15: “Does the patient have early morning awakenings?”

We scored the items as follows:

- For item 13, we gave a score of 0 if the patient had no problem, a score of 1 if the patient only had difficulty falling asleep a few nights in the past week and 2 if there was difficulty every night.
- For item 14, we gave a score of 0 if the patient had no problem and a score of 1 for restless and occasionally disturbed sleep. We gave a score of 2 if the

patient got out of bed in the middle of the night and/or had woken up every night in the past week.

- For item 15, we gave a score of 0 if the patient had no problem. If the patient woke up early, but then went back to sleep a score of 1 was given. We gave a score of 2 if the patient woke up earlier than usual and could not go back to sleep.

We used a cut-off score of ≥ 1 to describe sleep disturbances recognised by proxy-raters for items 13 and 14. For item 15, we used a cut-off score of $= 2$. We used item 13 as a measure of problems with sleep onset latency (SOL), item 14 as a measure of problems related to number of wake bouts (NoW), and item 15 as a measure of problems with early morning awakening (EMA). These measures were used when comparing the CSDD items and actigraphy measurements. It should be noted that the CSDD is not validated to measure sleep or sleep disturbances, but is a measure of depression. However, the questions listed above could still elicit valuable information about patients' sleep, as it is designed to identify depression-related sleep problems. To my knowledge, no prior studies have used the CSDD for this purpose.

4.3.5 Statistical analyses

The empirical investigation compared the results from two methods of measuring sleep: actigraphy and the proxy-rater based approach. We calculated descriptive statistics for all relevant variables. Furthermore, in order to investigate whether the measures yielded comparable results, we conducted three analyses. First, we conducted McNemar's tests to investigate if there were significant variances between the relevant measures. Cohen's kappa tests were used to investigate the degree of similarity between the pairs of relevant measures from actigraphy, the NPI-NH and the CSDD, respectively. Third, we conducted sensitivity and specificity analyses for all of the pairs of measures. For the sensitivity and specificity analyses, we developed receiver operating characteristics (ROC) curves. ROC curves are calculated by

plotting the true positive rate against the false positive rate for the diagnostic test. Each ROC curve has an AUC (area-under-the-curve) value, which indicates the performance for each pair of measures. AUC values can be assessed as follows: a value of 1 = a perfect test, a value of 0.97 = a very good test, values below 0.75 = not clinically useful and values close to 0.5 = no discriminatory value (Fan et al. 2006).

4.4 Methodological choices in papers 2 and 3

4.4.1 Design

Papers 2 and 3 are based on a large-scale, double-blinded, multicenter placebo-controlled randomised clinical trial. It reports the effects of pain treatment (paracetamol/buprenorphine) on actigraphy-measured sleep in people with dementia and depression. The results on sleep are secondary outcomes of an RCT that comprises both depression-related and sleep-related outcomes.

In paper 2, *Effects of Pain Treatment on Sleep in Nursing Home Patients with Dementia and Depression – A Multicenter Placebo-Controlled Randomised Clinical Trial*, we used actigraphic sleep data collected for 14 consecutive days. The first week served as baseline measurement while the second week was the experimental period. Thus, paper 2 investigated the short-term effects of pain treatment.

In paper 3, *Long-Term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-week Randomized Placebo-Controlled Trial*, we used actigraphic sleep data collected in the week before treatment commenced (baseline) and during week 13 of the treatment/placebo period. Thus, paper 3 investigated the long-term effects of pain treatment.

4.4.2 Setting, participants and data collection

The RCT was conducted between August 2014 and September 2016. I conducted the data collection together with Ane Erdal. We collaborated with physicians and nurses working at the 47 NHs. I will describe this process in detail, because it gives insight into how we took care of patients' interests and ensured high data quality.

The data collection process started with contacting the municipal agency for elderly and nursing homes with a short presentation of the project. Agency managers who were favourable to the project forwarded e-mails to managers at the different NHs. We in turn contacted the NHs directly and agreed on a date for the first visit at the NH, where we gave a 45 minute presentation of the project to management, physicians and nurses at the NH. Any questions or misgivings were followed up directly. These meetings were a good opportunity to get acquainted with staff and gave them a chance to discuss the project with us.

We then set a date for the second visit, during which we screened all patient journals in line with the list of inclusion and exclusion criteria. If there was sufficient time, we conducted a CSDD assessment. We took steps to discuss potential inclusion of patients who had scored equal to or above 8 on the CSDD. We discussed this with both the NH staff and the patient. If the patients were positive and the NH staff recommended inclusion, we called the patient's next of kin/legal guardian and explained the study protocol to them. We explained the study aims, intervention and time use. In cases where the next of kin was positive to inclusion, we distributed a letter with comprehensive information about the study. We asked the next of kin to give presumed consent if they thought that the patient would be positive to inclusion if s/he were able to understand the study more thoroughly. Next of kin/legal guardian, who agreed to inclusion, returned a signed letter of consent.

After informed or presumed consent was given, we contacted the NH and set a date for the third visit. We tried to make the visits as unobtrusive as possible for NH staff. This implies that we visited the NH when the primary nurse who was familiar with the patient was working. In the following process, we coordinated all of our meetings so that the assessment would put minimal strain on the NH staff. We aimed to conduct all relevant measurement during the third visit. When conducting the measurements, we sat with the nurse and provided guidance on the proxy measurement. This was done in order to avoid any confusion regarding the assessment tools and to ensure high compliance from the staff. The process took approximately 1.5 to 4 hours per patient. Since the nurses who served as proxy-raters had to be taken out of regular work during data collection, it arguably put a strain on the rest of the NH staff and their patients. Neither proxy-raters nor NH staff received any compensation for their participation.

During the third visit, patients who had CSDD scores below six were excluded. When all measurements were done and we had an overview of the medication list, we met with the NH physician. Based on the study protocol and the generated data thus far, we suggested either paracetamol or buprenorphine transdermal patch. We asked for the physician's opinion on inclusion and for any contraindications that would make inclusion unfeasible. We also emphasised that the physician was responsible for the treatment. If judged as necessary, we conducted interaction analyses using the online tool *www.interaksjoner.no* (formerly known as DRUID). If the physician agreed to inclusion and analgesics treatment, the medication was noted in the patient's medication chart with start and end date, type of medication and a number from the medicine package that indicated the allocation to treatment group. We told the physician and NH staff to be cautious regarding any potential change. We also told them to contact us 24/7 if there were any changes, or if there were any doubts regarding the treatment that implied that the medication should be discontinued immediately. In addition, we supplied NH staff with an envelope that they were

instructed to open in the event that they needed to know immediately whether the patient received active or placebo treatment.

During the fourth visit, we conducted the measurements for week six, which is not included in this thesis. During the fifth visit, we conducted the measurements for week 13. All of this was done in the same manner at 47 NHs in 11 different municipalities in Norway. During this period, data collection was a full time job for Erdal and me. We did the data collection independently of our supervisors and other research team members, but informed them about the number of patients included and any potential problems we faced during the process.

4.4.3 Inclusion and exclusion criteria

Patients were included if they were ≥ 60 years, long-term NH patients with > 4 weeks of stay. Importantly, depression and dementia were both inclusion criteria. We used the CSDD to assess depression. We required a CSDD score ≥ 8 for inclusion and allowed a fluctuation between 8 to 6 from screening to baseline. A cut-off point of 8/9 has the best accuracy for setting a diagnosis of depression in line with ICD-10 criteria (Barca et al. 2010). In papers 2 and 3, we used MMSE to assess possible dementia, and to be included, patients had to have a score of ≤ 20 (Pernecky et al. 2006; Kuhull et al. 1994).

In the actigraphy sub-project, we excluded patients if they did not want to wear an actigraph; were immobile or had involuntary movement; had paralysis in the arms or upper body or any form of chronic movement disorder; or were bed-ridden. Moreover, patients were excluded if they had cognitive impairment connected to other diagnoses than vascular dementia, Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia or mixed dementia; severe pain (MOBID-2 pain score ≥ 7); contraindication or clinically significant drug interaction to the assigned study treatment; life expectation < 6 month; suicide risk;

severe aggression (with NPI-NH aggression item ≥ 8); severe hepatic or renal failure; anaemia (haemoglobin < 8.5 mmol/L in men, < 7.5 mmol/L in women); uncontrolled epilepsy; severe illness not compatible with study participation; or planned treatments for any opioid analgesic additional to or exceeding buprenorphine 5 $\mu\text{g}/\text{hour}$ (for a tabular overview, see Table 1 in paper 2).

Of the 2323 patients from 47 NHs who were screened for potential inclusion, 162 were eligible to participate in the broader DEP.PAIN.DEM study. Of those 162 patients, the actigraphy sub-project reported on in papers 2 and 3 included 106 participants. Of the 106 patients, 49 were randomly assigned to the placebo group and 57 to the active treatment group. The flow chart in Figure 2 shows the full screening and inclusion process for the study:

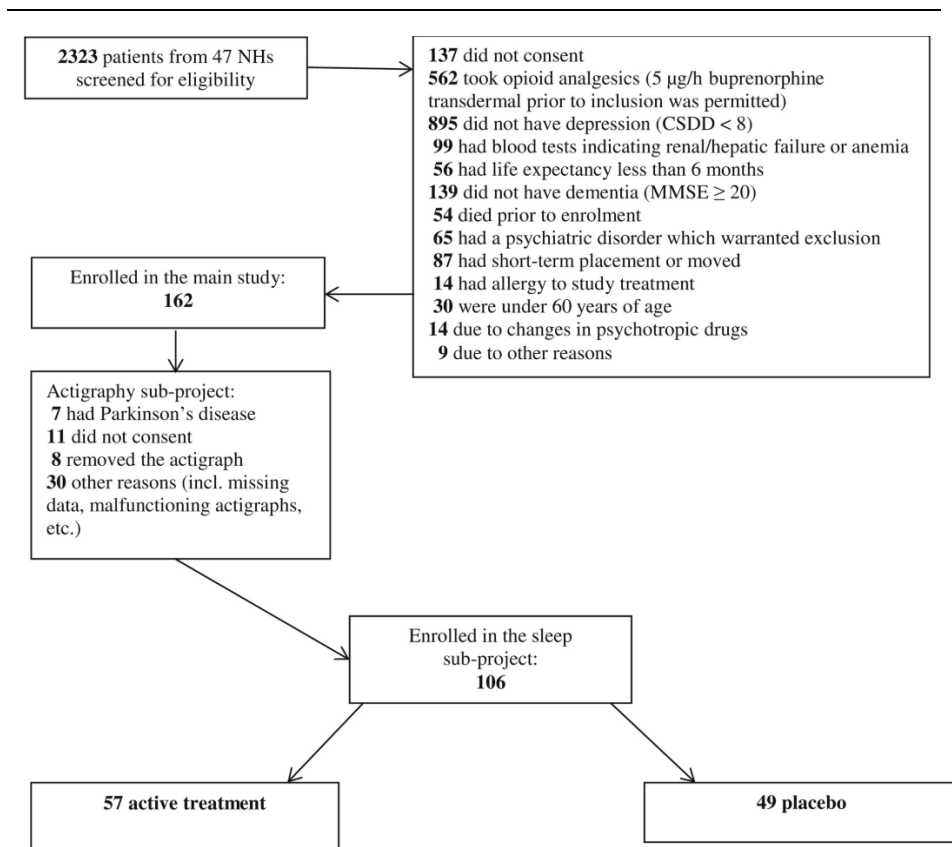


Figure 2: Flowchart showing screening and inclusion for paper 2 and 3 (reprinted from paper 2)

It is noteworthy that pain was not an inclusion criterion in the intervention study. This choice was made for several reasons. One of the reasons was that pain is particularly difficult to assess in people with dementia. In the RCT, we assessed pain with the assessment tool Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale (MOBID-2). The instrument has good validity, interrater reliability, internal consistency and responsiveness (Husebo et al. 2014). This assessment tool was used to investigate how pain developed during the 13 weeks (with measurement at weeks 0, 6 and 13). Furthermore, the assessment tool was used to exclude patients who had

a pain score of ≥ 7 or more at baseline. It would arguably have been unethical to include patients with high pain scores, since we would have had to be sure that these patients actually received active pain treatment rather than placebo. Furthermore, based on the above-mentioned pain-depression dyad, which suggests that pain and depression often coexist and exacerbate each other (Chopra et al. 2014), we assumed that depression could be an expression of pain. Finally, by not using pain as an inclusion criterion, we have larger variation in pain scores. This allows us to compare patients with and without probable pain, as measured with the MOBID-2. For these reasons, we chose not to use pain as an inclusion criterion.

4.4.4 Intervention

The patients received either paracetamol tablets/placebo tablets or buprenorphine transdermal system patch/placebo transdermal system patch. Paracetamol is one of the most used analgesic-antipyretic agents; however, the mechanism behind its effect is not fully understood (U.S. Food & Drug Administration 2017; Fellekatalogen 2017). Buprenorphine resembles morphine, but it is a partial agonist; its maximum effect is less than that of morphine, and it antagonises the effect of other opioids (U.S. Food & Drug Administration 2017; Fellekatalogen 2017). We allocated patients who were already taking paracetamol ≤ 1 g/day prior to inclusion to active or placebo paracetamol tablets max. 3 g/day. The study treatments were prescribed in addition to the basic dose by the NH physician. We assigned patients to active or placebo buprenorphine transdermal system 5 $\mu\text{g/h}$ (max. 10 $\mu\text{g/h}$) if they were taking non-opioid analgesics/paracetamol > 1 g/day, and/or NSAID/buprenorphine (5 $\mu\text{g/h}$). It is important to emphasise the results from a previously conducted study by Husebo et al. (2014), in which the intervention group (n=175) were subject to an eight-week stepwise protocol for treating pain. The medications used were paracetamol, pregabalin, morphine and buprenorphine. The study suggested that the buprenorphine/morphine was well tolerated, since only 4 of 40 participants who

received an opioid were withdrawn from the study as a consequence of adverse events (Sandvik et al. 2014).

We also assigned patients who had difficulty swallowing tablets to step 2 (see Table 1). On a fixed day every week, the buprenorphine transdermal patch/placebo patch was changed. This is in line with administrative guidelines (Felleskatalogen, 2019). Patients who were taking buprenorphine transdermal 5 µg/h prior to inclusion were given the study treatment as an additional 5 µg/h transdermal patch (active or placebo). After inclusion and study treatment start-up, patients continued their usual medical treatment (including any regular or “as needed” (PRN – pro re nata) analgesic. No new PRN were allowed.

	Regular analgesic treatment	Randomly assigned to either:	Dose
Step 1	No analgesics or paracetamol ≤ 1g/day	Paracetamol tablets	3 g/day
		Placebo tablets	Inactive placebo
Step 2	Non-opioid analgesics/paracetamol > 1 g/day, and/or NSAID*/or no analgesics - but with difficulty swallowing tablets	Buprenorphine transdermal system	5 µg/h (max. 10 µg/h)
		Placebo transdermal system	Inactive placebo

*Except low-dose acetylsalicylic acid

Table 1: Overview of how patients were assigned to treatments (reprinted from paper 3).

We advised clinicians to keep doses of psychotropic and analgesic drugs stable during the study period. This was done in an attempt to achieve stability and control over potential confounding variables. If any clinical changes occurred, they were to

be treated adequately. If this treatment interfered with the study, we excluded the patients in question and registered the reason for exclusion.

4.4.5 Outcomes

The outcome measures were different sleep parameters as measured with actigraphy. In paper 2, the sleep-related outcomes were total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO), early morning awakening (EMA) and number of wake bouts (NoW). In paper 3, we used the same sleep-related outcomes, but in addition, we measured daytime total sleep time (DTS). In paper 2, we registered activity continuously for 14 consecutive days, during which the intervention started on day eight. Thus, the first week of measurement constitutes the baseline. In paper 3, activity was registered continuously for seven consecutive days in week 13 of the treatment period, and compared to baseline data (which was one week prior to intervention, as in paper 2).

4.4.6 Statistical analyses

In paper 2, we calculated descriptive statistics for all relevant variables, which provided an overview of the characteristics of patients' sleep in the entire sample, as well as in each of the experimental groups. Furthermore, we conducted a mixed within-between subjects ANOVA (placebo versus active treatment and pre-treatment versus post-treatment) for all sleep outcomes. In addition, we assessed differences between pre- and post-treatment sleep outcomes within each treatment group, using paired t-tests for each of the experimental groups separately.

We also conducted several sub-group analyses for all sleep outcomes. The first sub-group analyses, mixed within-between subjects ANOVA, investigated only patients who had sleep disturbances at baseline, defined as $SE < 85\%$. In the second sub-

group analyses, we compared the effect of active and placebo treatment for patients, whose MOBID-2 score was ≥ 3 , i.e. patients who experienced pain at baseline. Finally, in the last sub-group analyses, we compared the effect of active buprenorphine to that of active paracetamol. We used *IBM SPSS Statistics 22* for all the statistical analyses in paper 2.

In paper 3, we similarly calculated descriptive statistics for all relevant variables and compared across the experimental groups. We chose linear mixed models that investigated the long-term effects (from baseline to week 13) of pain treatment for the main analyses in paper 3. This is because mixed models allow for regression-based analyses of treatment effects even in the case of considerable attrition, as long as data is missing at random (Bennett 2001). Thus, we can retain individuals with missing data at one time point in the analyses, which was valuable due to the attrition from baseline to week 13.

In addition to the main model, we conducted similar mixed model analyses for three sub-groups. First, we investigated patients with MOBID-2 score ≥ 3 . Second, we investigated patients with SE $< 85\%$. Third, we compared patients receiving active paracetamol and active buprenorphine treatment, respectively. We also conducted a 2x2 ANOVA analysis that included only data from the 58 patients who had complete data from week 13. We did this to explore if different analyses would give the same results. We used *IBM SPSS Statistics 24* for all statistical analyses in paper 3.

5. Main results

In this chapter, I briefly outline the main results of the three published papers. I summarise the results from *Clinically Significant Discrepancies between Sleep Problems Assessed by Standard Clinical Tools and Actigraphy* (paper 1), *Effects of Pain Treatment on Sleep in Nursing Home Patients with Dementia and Depression: A Multicenter Placebo-Controlled Randomised Trial* (paper 2) and *Long-Term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-week Randomized Placebo-Controlled Trial* (paper 3) in the three sub-sections below.

5.1 Paper 1

- Sleep disturbances were common among NH patients (n=83), and our results suggest that they were even more prevalent than what is found in earlier studies.
- Patients spend on average 12 hours and 20 minutes in bed.
- Using the NPI-NH, NH staff categorised 20.5% of patients as having sleep disturbances. This was significantly lower than the comparable objective actigraphy measurement of sleep, which indicated that 89.2% had sleep efficiency below 85% ($p<0.001$)
- Significantly more sleep disturbances relating to SOL, NoW and EMA were detected by actigraphy than by the CSDD sleep items (for all variables, $p<0.001$).
- The CSDD and NPI-NH measures had from very small to small probability for capturing the sleep outcomes detected by actigraphy recordings.
- When sleep was assessed with common clinical tools like the NPI-NH and the CSDD, sleep disturbances appeared to be underreported or unrecognised by NH staff, when compared with actigraphy measurement.

5.2 Paper 2

- In the full sample (n=106), SE (from 69.9% to 72.2%), SOL (from 31.7 min to 24.6 min), and EMA (from 50.1 min to 40.5 min) improved for the active treatment group compared to the placebo group from baseline to week 1 (SE: p=0.003; SOL: p=0.047; EMA: p=0.043).
- In the sub-group of patients with pre-existing sleep disturbances (SE < 85%) identified at baseline (n=89), the analyses revealed similar results as for the main effects. In addition, TST (from 477.7 min to 497.6 min) improved significantly for the active treatment group compared to the placebo group (TST: p=0.014).
- There were no significant differences between active and placebo treatment for any of the sleep outcomes for the sub-group of patients who experienced pain at baseline (n=46).
- There was a significant increase in TST (from 502.3 min to 534.0 min) for patients who received active buprenorphine (n=30) compared to those who received active paracetamol (n=25) (TST: p=0.016).

5.3 Paper 3

- We found no statistically significant differences between patients who received active pain treatment and those who received placebo treatment when analysing the full sample (n=106) from baseline to week 13.
- In the sub-group of patients with pain at baseline, i.e. MOBID-2 scores ≥ 3 (n=46), there were no statistically significant differences between the patients who received active treatment and those who received placebo treatment.
- The analyses for the sub-group of patients with SE < 85% (n=90) showed no statistically significant differences between the patients who received active treatment and those who received placebo treatment.

-
- The analyses for the sub-group of patients receiving the two different types of active pain treatment (n=57) revealed that TST (from 508.7 min to 580.6 min) and SE (from 68.7% to 77.4%) were both improved after 13 weeks for patients who received active buprenorphine compared with patients who received active paracetamol (TST: $p=0.01$; SE: $p=0.03$).

6. Discussion

In this chapter, I discuss the findings of the three papers. First, I discuss strengths and weaknesses of the methods employed in the studies. Second, I discuss interpretations and implications of the results. Finally, I discuss ethical considerations related to the empirical investigation.

6.1 Discussion of the methods

The studies aimed to investigate the degree to which actigraphy-based and proxy-rater based assessments of sleep in NH patients provide comparable clinical outcomes, and the short-term and long-term effects of pain treatment on sleep in NH patients with dementia and depression.

We based paper 1 on secondary cross-sectional analyses of baseline data from a comprehensive RCT (Husebo et al. 2019) and papers 2 and 3 on a placebo-controlled, double-blinded RCT. In the sample for paper 1, we included both people with and without dementia. In papers 2 and 3, we included only people with possible dementia as measured with MMSE. All of the three studies employ actigraphy to measure sleep, and we recorded all socio-demographic variables from patients' medical journals. In addition, we used the MMSE and the CSDD in all of the studies. In paper 1, we used the NPI-NH, and in papers 2 and 3 we used the MOBID-2 to measure pain.

The comprehensive work related to conducting the three studies in the clinical setting demonstrates the complexity of the challenges that NH staff faces every day trying to give the best possible care for patients. The nature of the studies, their different objectives and the differences between the data in the three studies made it necessary

to employ a set of different statistical analyses. In the following, I discuss the selected research design and methods for the each of the papers.

6.1.1 Discussion of the methods used in paper 1

Cross-sectional design

We based this paper on secondary analyses of baseline data, which implies that the study has a cross-sectional design. Given a representative selection, cross-sectional studies are often used to study prevalence, i.e. the number of cases in a population at a given point in time (Mann 2003). They can, however, also be used in comparative designs. Knowledge on the prevalence of sleep disturbances in NH patients is crucial for clinicians, since it provides information on the likelihood of sleep being a concern for the patient.

Cross-sectional studies have several advantageous characteristics: they can generate information about many different variables and they can be effective in order to generate hypotheses (Rothman et al. 2008). However, their application is less useful to study causal and longitudinal relationships. Validated assessment tools or questionnaires are often used in cross-sectional studies (Mann 2003). In paper 1, we measured the sleep-related items in the NPI-NH and the CSDD and other descriptive data at the same time (baseline). The variables generated from the actigraphy data, however, reflect the mean score from activity/inactivity measured for seven consecutive days. Thus, we based the baseline score in actigraphy on average sleep assessments during one week.

Selection bias

The COSMOS study population of 545 patients distributed across 67 NH units is a reasonably representative selection. The actigraphy sub-project included 83 patients for whom we had NPI-NH, CSDD and actigraphy measurements. Since we conducted actigraphy measurement in a sub-project comprised in the COSMOS project, we had to make a choice regarding which patients to include. We primarily made the decision based on the inclusion criteria. However, due to financial issues, i.e. the high monetary cost associated with acquiring actigraphs, we could not offer actigraphs to all patients who could potentially be included. Ideally, we would be able to offer actigraphs to more patients. The chosen solution was to offer actigraphs to the first ten patients in every NH unit. Thus, there was no true randomisation process in the selection of patients who were offered actigraphy measurement. The absence of true randomisation increases the risk of selection bias. We explored the likelihood of selection bias by investigating if there were statistically significant differences in baseline scores for relevant variables (age, MMSE sum score, CSDD sum score, gender, NPI-NH sum score) between the actigraphy sample (n=83) and the remainder of the study sample (n=462). We found no statistically significant differences, which suggests that the included patients were representative for the population under investigation on observed characteristics. We therefore concluded that the risk of selection bias was reasonably low.

Challenges with the use of proxy-raters

We used proxy-raters to collect data using the NPI-NH and the CSDD. As previously mentioned, a proxy-rater is a person who knows the patient well and who is consequently able to answer on the patient's behalf (Pickard and Knight 2005). Proxy-raters are usually used when a respondent is not able to give valid self-report, which is often the case for people with dementia (Husebo et al. 2014b). There is,

however, a risk that using proxy-raters may increase the chance of information bias. This occurs in instances in which the rater consciously or unconsciously gives incorrect information, which in turn is registered as part of the data (Rothman et al. 2008). The answers given by the proxy-rater may be influenced by the rater's own perceptions and feelings (Snow et al. 2005). In addition, the results from the NPI-NH and the CSDD may be affected by recall bias. The answers given on the different assessment tools rely on the rater ability to recall past events (Althubaiti 2016). This can be challenging when assessing sleep using tools such as the NPI-NH and the CSDD.

Night-time workers, who had primary insight into patients' sleep during the night, conveyed information about patients to daytime workers, who in turn reported on patients' sleep to the research team. This is how it is typically done in Norwegian NHs. Every morning, NH staff members sit down together and discuss each patient (whether any changes have occurred, how the patient has been sleeping etc.). In the event of no oral report being given, daytime staff reviews the report written by the night-time workers. This could potentially lead to information bias, for example due to misinterpretation or poor communication. We cannot correct for this in our research design, and it should consequently inform the interpretation of our results. If the COSMOS study was designed with the aim of the current study in mind, we would have done this differently, for instance the study would have benefitted from proxy-rating by night-time workers.

Weaknesses related to the use of the CSDD to measure sleep

One may also question the validity of the CSDD for measuring sleep disturbances, since the instrument is primarily developed to assess depression in people with dementia. While we are fully aware that these questions are not validated to measure sleep in this patient group, the sleep-related questions in the CSDD likely give some

relevant information about the proxy-rater's perception of patients' sleep. Interestingly, Jeon et al. (2015) demonstrated that the CSDD has limited value when administered by NH staff. This goes against prior findings suggesting that the instrument has high validity and reliability (Barca et al. 2010). Jeon et al. (2015) argued that the complexity of the scale and the time required collecting relevant information (in order to enable NH staff to assess the questions) were too comprehensive for proper use in a busy NH setting. It is reasonable to assume that this also applies to the use of the sleep-related items in the CSDD. It should be noted that the conclusions drawn by Jeon et al. (2015) are built on one single study, and there is arguably need for further empirical investigation of this question. Taken together, this implies that we need to interpret the results from the CSDD assessment with these limitations in mind.

Comparing proxy-rated sleep with actigraphy-based sleep outcomes

In paper 1, we used actigraphy as the reference point, which implies that we view it as a “gold standard” compared to the sleep-related items in the CSDD and the NPI-NH. However, one can argue that actigraphy only gives an overview of activity versus inactivity. In light of what we know about the population under investigation, who lives under institutional care with little room for activity, the results from paper 1 must be interpreted with caution. In addition, it should be noted that previously conducted studies show that actigraphy is less accurate in distinguishing sleep from wakefulness when sleep efficiency is reduced (Kushida et al. 2001; Sivertsen et al. 2006). Importantly, when detecting wakefulness, actigraphy has low specificity (36.3%), while its sensitivity for detecting sleep is high (95.2%). In paper 1, 89.2% had sleep efficiency below 85%, which implies that sleep as measured with actigraphy may overestimate the amount of time patients are actually sleeping. Moreover, as stated in paper 1, this means that the sensitivity for sleep as measured with the sleep-related items in the CSDD and the NPI-NH may be even lower than suggested by the results from paper 1.

Furthermore, in relation to paper 1, the nature of the study does not allow for concluding on the question of whether the divergence between actigraphy recordings and proxy-rater assessments was due to the rating instruments or due to the raters. However, this would be an interesting topic for future research.

6.1.2 Discussion of the methods used in papers 2 and 3

Randomisation and blinding process

Papers 2 and 3 are based on a 13-week double-blind, placebo-controlled, randomised clinical trial. RCTs are considered to provide the most reliable evidence on the effectiveness of interventions (Kendall 2003; Akobeng 2005), because their characteristics largely eliminate the risk of confounding factors influencing the outcome. No members of the research team were involved in the production of the randomisation list. There was no use of stratification factors. While randomisation can limit the chance of selection bias, it does not guarantee that the experimental groups are identical with regard to patient characteristics (Akobeng 2005). This implies that there can still be unobserved, confounding variables. In the attempt to avoid confounding variables, stratification factors are widely used. Examples of such factors can be important and different prognostic features that may serve to generate separate block randomisation lists (Akobeng 2005). All of the included patients in the DEP.PAIN.DEM project were offered actigraphs if they fulfilled all of the above-mentioned inclusion criteria and none of the exclusion criteria for the actigraphy sub-project. This implies that the patients were randomised to active or placebo treatment before we knew if they were included in the sleep sub-project (see the flow chart on p. 46). 57 patients who were randomised to active treatment and 49 patients randomised to placebo treatment was included in the sleep sub-project. We found no statistically significant differences between the two groups (active versus placebo) when we analysed baseline data for systematic differences. This suggests that the

randomisation holds reasonably well despite this minor asymmetry in the two experimental groups.

To ensure double blinding of the study, a statistician provided the research team with a blinded, sequential list of pack identification numbers. We assigned patients consecutively to the next pack number in the list when they were included in the study. The packages with active/placebo buprenorphine transdermal system or paracetamol were identical. The paracetamol tablets were purchased from Kragerø Tablettproduksjon AS, Norway, while Mundipharma Research Limited, UK provided buprenorphine transdermal system. These companies were otherwise not involved in the study. It was not possible for patients, NH staff or members of the research team to know if the patient received placebo or active treatment. If the patient or NH staff had known which treatment the patients received, it could affect the assessment and by extension the results.

Internal validity and bias

Internal validity is a central measure of the quality of RCTs. Studies have high internal validity when it is possible to attribute observed differences between the groups to the intervention under investigation (Akobeng 2008). Two important types of error threaten internal validity: systematic errors and random errors. In clinical trials, there are four main sources of systematic error: selection bias, performance bias, detection bias and attrition bias (Akobeng 2008; Keirse and Hanssens 2000). Successful randomisation eliminates selection bias, which results in the control group and the treatment group being very similar in relevant characteristics at baseline (Kendall 2003; Akobeng 2008). Thus, one would expect that treatment effects are not due to confounding factors.

Performance bias occurs when there are systematic differences in the provision of care to the groups under investigation, or the exposure to other factors that could influence measured outcomes (Akobeng 2008). For instance, if NH staff in our study had not been blinded regarding which patients were in each of the treatment groups, it could influence their treatment of the patients. This could in turn have influenced patients' sleep. Performance bias is slightly different from the well-known Hawthorne effect, i.e. that participants may consciously or unconsciously modify their behaviour due to being observed (Goodwin et al. 2017). The fact that we blinded NH staff mitigates the risk of performance bias in our study.

Detection bias refers to systematic differences between groups with regard to how outcomes were assessed, in particular the assessment of subjective outcomes. If raters have knowledge about treatment allocation, it could influence their assessment of the condition of patients (Akobeng 2008). We avoided such issues in papers 2 and 3 by using objective outcomes (actigraphy) and masking NH staff regarding the allocation of treatments. This limits the potential effect of both performance bias and detection bias. Since the study is double-blinded and the randomisation was successful, we conclude that these issues pose no significant threats to internal validity in papers 2 and 3.

Attrition bias occurs when there are systematic differences between the experimental groups with regard to the loss and withdrawal of participants (Akobeng 2008). In the period investigated in paper 2, i.e. from baseline to week one, two patients were withdrawn from the study because of adverse reactions to buprenorphine. Such limited attrition is very unlikely to result in systematic differences. However, in paper 3, 48 patients dropped out from baseline to week 13 of the treatment period. This creates a risk of systematic differences between patients who dropped out and those who completed the study period. However, as discussed in the following, we used statistical analyses that attempt to remedy the problems of attrition.

Dealing with missing data

In paper 3, we based the main empirical investigations on linear mixed model analyses. Such analyses are appropriate in light of the substantial missing data for actigraphy measurement in week 13. Mixed model analyses make it possible to conduct regression-based analyses for treatment effects, even in the event of considerable attrition. This is due to the method allowing for retaining data for subjects that have missing data for one or more important variables (Bennett 2001). However, the usefulness of the method and its ability to tackle the problems related to attrition rely on the type of missing data, i.e. data must be missing at random.

To examine if this assumption held, we investigated and compared baseline characteristics (age, gender, CSDD score, MOBID-2 score, NPI-NH score and MMSE score) between patients who dropped out of the study (n=48) and those who completed the study (n=58). The results showed no statistically significant differences in any of the relevant baseline characteristics. This strengthens the case for assuming that the data was missing at random. The implication is that one can infer that potential treatment effects do not rely on the mechanism that caused the missing data (Bennett 2001). However, we should note with caution that there could be other systematic differences, for instance in these patients' reactions to treatment, or in other unobserved factors that appeared after we conducted baseline measurement.

Sleep as a secondary outcome

The study was not designed with sleep as its primary outcome. This implies that we did not include only patients with sleep disturbances or differentiate between different kinds of sleep disturbances. Instead, we included all patients who met the inclusion criteria, regardless of whether they had sleep disturbances or not, and of the potential underlying causes thereof. Different sleep disturbances require different

types of treatment, which was not taken into account in the design of the study. However, the aim of papers 2 and 3 was to investigate the short-term and long-term effectiveness of pain treatment on sleep in people with dementia and depression. The results for the depression outcome in the broader study, which is reported by Erdal et al. (2018a), showed that analgesic treatment did not reduce symptoms of depression. These results have implications for the interpretation of the results included in the present study. As previously mentioned, studies investigating the relationship between sleep, pain and depression in people without cognitive impairment have shown that depression can be a mechanism through which pain leads to sleep disturbances (Niacassio et al. 2012; Valrie et al. 2007). Our rationale was that there is an interactive relationship between depression, pain and sleep, and that they may reciprocally influence each other. Since symptoms of depression were not reduced in the group of patients who received active pain treatment (Erdal et al. 2018a), the results from papers 2 and 3 can mainly be seen as generating new hypotheses for further research.

Type I and II error

In papers 2 and 3, we risk type 1 errors due to our reliance on multiple outcome measures (SE, SOL, EMA, WASO, NoW, TST, DTS). Using multiple outcomes without correcting for multiple comparisons increases the risk that significant effects are found for one or more outcomes, even when in fact there are none. As stated on p. 668 in paper 2, *“we did not correct for multiple comparisons in our study. However, a simple Bonferroni correction would be overly conservative and would increase the risk of type II errors. Therefore, we urge the reader to take the lack of such correction into account in the interpretation of the findings of the study.”*

The Bonferroni correction, discussed by e.g. Zhang et al. (2001), implies dividing the p-value significance threshold (0.05) by the number of hypotheses tested (in the case of paper 2, six outcome measures). For our study, this would give a Bonferroni

critical value of $p = 0.0083$. In our main results, this would imply that only the SE result, i.e. one of three statistically significant results, would remain significant. However, as pointed out by Feise (2002, p. 2), an objection to such adjustment is that “if you reduce the chance of making a type I error, you increase the chance of making a type II error”. Such an approach could be too conservative. An alternative approach would be to merge these measures into one global test statistic (see e.g. Pocock 1997). However, these measures cannot easily be transformed in this way, since they are a combination of measures capturing short time periods (e.g. EMA), long time periods (e.g. TST), percentages (e.g. SE) and numbers/frequency (e.g. NoW).

Regarding adjustments of p-values, such efforts are complicated by the fact that our investigation includes repeated measures, as pointed out by Bender and Lange (2001). Finally, it is possible to treat each of the outcome variables as different facets of the phenomenon worthy of equal interest in the empirical investigation (cf. Pocock 1997). There are several previous studies with comparable designs (e.g. Fetveit and Bjorvatn 2004; Taibi et al. 2009) that report a similar set of outcome variables without correcting for multiple comparisons. It is, in any case, important to consider this potential limitation when interpreting the findings in papers 2 and 3.

External validity

The results of an internally valid RCT may be limited if the study results are not applicable to the broader population of patients. External validity concerns the degree to which the results of a study provide evidence that can be generalised beyond the study and applied in other similar clinical circumstances (Akobeng 2008). If external validity is high, results can be generalised into similar settings in the “real world” (Akobeng 2008).

The comprehensive combination of inclusion and exclusion criteria in papers 2 and 3 is cause for some concern. In particular, the inclusion criteria requiring that patients had to be depressed according to the CSDD and not prescribed any opioid analgesics (5 µg/h buprenorphine transdermal prior to inclusion was permitted) made it difficult to recruit patients to the study. Furthermore, the patients had to have dementia according to the MMSE (cut-off score < 20). Combined, these criteria account for 1596 of the 2323 excluded patients. Therefore, the final sample is quite sub-selected relative to the broader population.

When conducting mixed model analyses, we estimated intraclass correlation coefficients (ICC), which give an indication of the dependency of the patients belonging to the same NH. That is, ICCs provide information on the dependency of patient observations within the same NH (same medical doctor, same nurses etc.) (Twisk 2006). Our preliminary ICC analyses showed that observations within units were not significantly clustered within the NH units. We therefore conducted mixed models with random intercept. In the present study, it could be argued that NH patients with depression and dementia are the relevant population to which the results may be generalised.

Based on this evaluation, we conclude that the studies have reasonably good internal and external validity, although there are some issues discussed above that should inform the interpretation and evaluation of the results.

6.2 Discussion of the results

In the following, I discuss important aspects of the results in the three papers: First, I discuss the clinical usefulness of proxy-rater assessment. Second, I discuss how to identify sleep disturbances in NHs. Third, I discuss the subjective value of the improvement in sleep outcomes. Finally, I discuss whether we should recommend pain treatment for such disturbances.

6.2.1 Are proxy-rater assessments of sleep clinically useful?

Paper 1 suggests that sleep disturbances were underreported or unrecognised in proxy-rater assessments by NH staff. This is an important finding, since it raises questions about the usefulness of this approach for detecting sleep disturbances in NH patients. It therefore leaves us questioning whether proxy-rater tools are adequate for assessing sleep in people with dementia.

Valid proxy-rater assessment of sleep disturbances could provide useful information for the treatment of such disturbances. Selbæk et al. (2012) investigated the Norwegian version of the NPI-NH and concluded that it is reliable and valid for assessing psychiatric symptoms in NH patients. In paper 1, we investigated one of the items from the NPI-NH – item 11, which assesses sleep disturbances. Even though measuring sleep with actigraphy also has its limitations, the divergence between the outcomes is striking.

One of the results from paper 1 shows that patients spend on average 12 hours and 20 minutes in bed (from lights off in the evening to lights on in the morning). This is in line with previous findings (Fetveit and Bjorvatn 2002). Spending this amount of time in bed may enhance the likelihood of pain, wound development, hunger, and the feeling of being isolated. The study design does not allow us to investigate whether the patients were in bed for that amount of time because they wanted to, or if it was necessary due to institutional constraints. Either way, it may be harmful spending such an amount of time in bed, and obviously one cannot expect the patient to be sleeping for such a long period. In light of the time spent in bed, it is not surprising that almost 90% of patients had SE below the cut-off of 85%. We compared actigraphy measurement of SE with measurements of item 11 in the NPI-NH, which reads: *“Does the patient have sleep problems? Is s/he awake during the night? Does s/he wander during night-time, getting dressed, or go into the room of others?”* This

comparison could yield suboptimal results, since SE is likely based on an inflated amount of time spent in bed, which translates into low SE.

Actigraphy data do not provide information on several factors captured by item 11 in the NPI-NH, such as whether patients wander during night-time or go into other patients' rooms. However, patients engaging in such behaviours would likely be assessed by proxy-raters as having night-time sleep difficulties. Thus, their NPI-NH item 11 score would correspond with low actigraphic SE. Therefore, we argue that the comparison between the two measurements at least provide some valuable information for clinicians and researchers.

The CSDD items used in paper 1 are validated for measuring depression rather than sleep, but contain quite specific items regarding sleep. Yet, the results show significant discrepancies between the sleep-related items in the CSDD and actigraphy. This contrasts with findings by Fetveit and Bjorvatn (2002), who found consistency between NH staff observations of SOL and EMA and actigraphic measurements. We should note that NH staff who were proxy-raters in the Fetveit and Bjorvatn (2002) study observed and noted rise and bed times, which is arguably likely to provide more awareness of patients' sleep. For this reason, those results are not quite comparable to the findings from paper 1 in this study. Meanwhile, the results from Fetveit and Bjorvatns's study suggest that increased focus on patient's bed routines may improve proxy-rated sleep assessment.

An additional issue with the proxy-rater sleep measurement is that daytime workers served as proxy-raters. However, the information about patients' sleep had been conveyed to them from night-time workers, who were likely to observe disturbed sleep in mobile or vocalizing patients. This communication might be influenced by several unobserved factors, such as the relationship between the workers, time pressure, noise, bias and so on. Moreover, it might be that information about the patients who most demanded the night-workers attention and care were over-

represented in information conveyed to the daytime workers. The proxy-raters thus at best reported indirect perceptions of patients' night-time sleep. Nevertheless, this may represent how patients' sleep is assessed in the nursing home setting.

To summarise, actigraphy, the CSDD and the NPI-NH are not optimal tools for measuring sleep in people with dementia. The CSDD is developed to measure depression, while the NPI-NH is developed to measure the presence and severity of different neuropsychiatric symptoms including sleep. To use actigraphy as a reference is also questionable. In paper 1, we used several cut-offs to identify sleep disturbances. However, when the patients spend more than 12 hours in bed, the meaning of the different sleep parameters and cut-offs become uncertain. So when this sub-section asks whether proxy-rater assessments are clinically useful, it is important to acknowledge the weaknesses associated with the different assessment methods used in paper 1.

Furthermore, we cannot assume that sleep is assessed on a regular basis in the NH, and there is currently no optimal method to assess sleep in this patient group. In paper 1, we state that the NPI-NH and the CSDD are common clinical tools. However, to what degree these instruments are actually used is uncertain. However, based on experience, we expect that to the extent that sleep is assessed, the NPI-NH and the CSDD are used or looked at for inspiration. Currently, actigraphy is arguably the best method to measure sleep objectively in people with possible dementia (Ancoli-Israel et al. 1997; 2003). As pointed out in paper 1, when sleep was measured with the NPI-NH and the CSDD, sleep disturbances were clearly underreported or unrecognised by NH staff, when compared to actigraphy. It is, however, unclear whether this reflects that the instruments poorly measure sleep, that the cut-offs used in the actigraphy setting are too uncertain, or that the NH staff does not recognise sleep difficulties.

6.2.2 How should NH staff identify sleep disturbances?

Our studies demonstrate the difficulty of the dual tasks of identifying and treating sleep disturbances in NH patients. Since proxy-rater measurement has low degree of agreement with actigraphy, it makes us question what else can be done. NHs are demanding workplaces, and it would be very valuable to have reliable assessment tools for NH staff to use in the everyday pursuit of good, evidence-based care and medical treatment to patients.

Our findings leave us questioning the value of the sleep-related items in the CSDD and the NPI-NH to measure sleep in NH patients. Although some studies recommend actigraphy as a supplement to proxy-rater assessment (see e.g. Most et al. 2012), it is likely too time-consuming and costly for measuring sleep in NH patients.

A potentially beneficial instrument in research and the clinical setting is the SDI – an expanded version of item 11 in the NPI-NH. A study conducted by Tractenberg et al. (2003) showed that the instrument correlated with actigraphy-derived sleep measurement, except for 24-hour measurement of TST and DTS. However, in that study, live-in caregivers evaluated sleep in persons with Alzheimer’s disease who were living at home. A potentially fruitful avenue for future research would be to examine the clinical utility of the SDI also in the NH setting. A potentially beneficial idea would be to have systematic routines for observations during night shifts, also including sleep diaries.

6.2.3 Pain treatment increased sleep as measured with actigraphy, but did patients sleep better?

In the RCT reported in papers 2 and 3, we used actigraphic measurements to investigate the effects of pain treatment on various sleep-related outcomes. In short,

pain treatment improved sleep (specifically, SE, SOL and EMA) in the shorter term, but these effects did not sustain in the longer term. However, we found an increase in TST (short-term and long-term) and SE (long-term) in patients receiving active buprenorphine treatment compared to active paracetamol. The rationale behind papers 2 and 3 was based on growing support of the hypothesis that pain, depression and sleep disturbances are linked and exacerbate each other (Senba et al 2015; Chopra et al. 2014; Finan et al. 2013), and may be alleviated by pain treatment (Husebo et al. 2013). However, neither pain nor sleep disturbances were inclusion criteria in the present RCT. If pain and sleep disturbances had been inclusion criteria, it would allow us to examine the relationship more thoroughly. Furthermore, our research design does not allow us to ascertain how symptoms of depression may have influenced the effect of pain treatment on sleep, since we did not compare patients with and without such symptoms. Importantly, however, as discussed in section 4.4.3, using the additional inclusion criteria of pain and sleep disturbances would cause other problems. These include threats to generalisability as a consequence of an even more sub-selected sample, and challenges for the randomisation of active and placebo medication, since allocating patients with pain to placebo medication would be ethically questionable.

In addition, we cannot conclude that the significant improvement shown with actigraphy represents a subjective improvement for the patient. To examine this, it would have been necessary to rely on self-reported data in cases where this was possible to collect. In cases where such self-reported data had not been attainable, it would have strengthened the study to include sleep diaries. As discussed above, proxy-raters should seek to observe patients during the night. This could potentially give additional and valuable information on patients' subjective sleep experiences.

Among the patients included in our RCT, some may have experienced pain and others not. As shown in papers 2 and 3, we had to screen 2323 patients from 47 NHs in order to include 162 patients with indication of dementia as measured with the

MMSE and depression as measured with the CSDD. Having pain and sleep disturbances as additional inclusion criteria would necessitate screening even more patients, which in turn would have demanded even more resources in the data collection process. Since we did not have pain as an inclusion criterion, we conducted sub-group analyses in which we only included patients who experienced pain at baseline. However, no effect of pain treatment on sleep was found. Importantly, the sub-group of patients with pain, dementia and depression was small (n=46), and these are secondary analyses.

It should be noted that the prescription of all opioids to NH patients in Norway has increased from 11% in 2000 to 24% in 2011 (Sandvik et al. 2016). Buprenorphine, which arrived on the Norwegian market in 2005, has been found to be prescribed to 10.5% of 1542 Norwegian NH patients with dementia (Sandvik et al. 2016). In a recent study that investigates opioid prescription use in NH residents with advanced dementia, the prevalence of strong opioid prescription was 19.3%. As pointed out by Sandvik et al. (2016), there was a stark increase in the prescription of strong opioids like fentanyl, buprenorphine, morphine and oxycodone to NH patients from 2000 to 2011. Despite the use of opioids, 79.4% of those patients were still experiencing signs of pain (Griffioen et al. 2017). These findings suggest that more studies investigating the potential effect of these medications in this particular patient group are necessary.

A potential explanation for the results in papers 2 and 3 is sedation. Sedation is a common adverse effect of buprenorphine which has been found to affect approximately 29% of the patients over the age of 65 with and without dementia (Pergolizzi et al. 2017). Erdal et al. (2018b) found that nine participants receiving active treatment were excluded from our RCT because of symptoms of sedation. Furthermore, patients who received buprenorphine had a significant reduction in daytime activity as measured with actigraphy (Erdal et al. 2018b). This indicates that the patients were affected by sedation.

To summarise, we found that pain treatment had an effect on sleep outcomes in the short term; however, the underlying mechanism is unclear. We cannot conclude unequivocally why we found such effects. It is moreover uncertain whether the changes were of subjective value for patients, which is a highly important question. Although we did find changes in a positive direction in several sleep parameters among patients who received active treatment in the short-term, we do not have conclusive evidence that patients in fact slept better.

6.2.4 Can pain treatment be recommended to improve sleep?

Although our results show that pain treatment had beneficial effects on some sleep parameters in the short-term, we cannot generally recommend pain treatment for improving sleep in these patients. This would require more conclusive evidence that the treatment actually improved sleep. Furthermore, an important aspect to take into account is the comprehensive attrition between week one of the treatment period and week 13 in our study. The total attrition was 48 patients, and it was most prevalent in the group of patients who received active buprenorphine (n=22) as compared to active paracetamol (n=13). The results from Erdal et al. (2018b) also highlight this – in particular the finding of significantly higher discontinuation due to adverse events in patients who received buprenorphine. This could be an indication that low tolerance for buprenorphine was one of the reasons for attrition. If so, this is a further argument against the use of such medication to improve sleep.

Treating sleep disturbances in this very fragile group of patients is challenging and important. Successful treatment may improve daytime functioning and quality of life, and it may possibly slow the progression of dementia (Kinnunen et al. 2017). The previously mentioned Cochrane review investigated the effect of light therapy for improving cognitive function, activities of daily living, sleep, challenging behaviour, and psychiatric disturbances in dementia (Forbes et al. 2014). Another recent Cochrane review investigated the effects of drug therapy (melatonin, trazodone or

ramelteon) compared to placebo for sleep disorders in people with dementia (McCleery et al. 2014). However, the conclusions are quite disappointing. In the first review, no effect was found of light therapy on sleep. In the second review, a distinct lack of evidence to help guide drug treatments was discovered. A concern is that if the source of sleep difficulties is due to changes in the brain caused by dementia, it is not clear if treatment with common drugs is effective in this particular patient group (McCleery et al. 2014). Meanwhile, positive effects of bright light treatment was reported in an above-mentioned meta-analysis of the effect of such treatment on different types of sleep problems, including sleep problems associated with dementia (Van Maanen et al. (2016) . Moreover, a recent meta-analysis, which only included RCTs on the effects of light therapy in dementia and mild cognitive impairment, reported moderate effect sizes on both behavioural disturbances and depression and a small effect size on total sleep (Chiu et al. 2017).

6.3 Ethical considerations

Patients with different levels of cognitive impairment took part in the studies. Doing research that includes people with cognitive impairment gives rise to research-ethical concerns, since these patients have reduced ability to understand the aim of the studies and the effort required to partake. Prior to data collection, we discussed patients' medical decision-making capacity with NH staff familiar with them. Based on this evaluation, we attempted to modify information about the studies and the effort required to be part of the study.

For patients evaluated to lack the ability to give informed consent, presumed consent was obtained through direct conversation with their legal guardians. Legal guardians (usually family members) were encouraged to evaluate if they thought the patients would like to take part if they had had the ability to understand fully the aim of the study. This implies that we cannot be sure that some patients included in the study did not want to partake, since they had reduced capacity to express their own preferences.

In light of this, one could argue that it might not be appropriate to conduct research in this fragile group. However, one can conversely argue that exactly because this patient group is fragile, the potential value of generating effective treatment justifies the burden on participants. With regard to paper 1, the Regional Committee for Medical and Health Research Ethics West Norway approved the COSMOS trial (REK 2013/1765). The trial is registered at www.clinicaltrials.gov (NCT02238652). With regard to papers 2 and 3, the Norwegian Medicines Agency (EudraCT 2013-002226-23) and the Regional Ethics Committee West (REC-West 2013/1474) approved the DEP/SLEEP.PAIN.DEM study. The study's Clinical Trial number is NCT02267057.

The World Medical Association has developed the Declaration of Helsinki (World Medical Association Declaration of Helsinki 2013). This declaration is a statement of ethical principles for medical research involving humans. The declaration states that *“medical research with a vulnerable group is only justified if the research is responsive to the health need or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research”* (World Medical Association Declaration of Helsinki 2013). In addition, the Declaration states that when research is conducted with people who cannot provide informed consent, such consent has to be provided from a legally authorised representative. In our data collection process, we made it clear that that we wanted close contact with nurses who knew the patients well and who were sensitive to any signs from the patients implying that they did not want to partake. From baseline to week 13, 48 of 106 patients dropped out of the study. Importantly, this number also reflects that we were following the process closely and that the risk/benefit balance was carefully considered.

A violation of the DEP/SLEEP.PAIN.DEM protocol was discovered during the first committee's evaluation of this thesis (after the data collection was completed). In the

DEP.PAIN.DEM trial, the Norwegian Medicines Agency approved the use of buprenorphine in the stepwise protocol, with the condition that no participants would receive an opioid analgesic as part of the trial unless they already received other scheduled analgesic treatment (e.g. paracetamol). However, as described in Table 1 in section 4.4.4, we allowed for prescribing buprenorphine/placebo transdermal system to participants who did not use any analgesic, but had difficulty swallowing tablets. This procedure is in line with common clinical procedures and previously published papers (Husebo et al. 2013). In retrospect, we found that three patients had received active buprenorphine while not having received analgesics at baseline, as shown in Table 2.

	1	2	Total
Treatment (1=active, 2=placebo)	57	49	106
Type of drug (1=buprenorphine, 2=paracetamol)	58	48	106
Received buprenorphine (1=active, 2=placebo)	31	27	58
Received active buprenorphine and no analgesics at baseline (1=yes, 2=no)	3	28	31*

**Note: In Table 5 in paper 2, we report results for 30 patients who received active buprenorphine. The reason for the discrepancy between the number reported here (n=31) and the number reported in Table 5 (n=30), is that one patient dropped out in week 1. This is also accounted for in paper 2.*

Table 2: Allocation of patients to treatments in the SLEEP.PAIN.DEM actigraphy sub-project

This information was provided to the Norwegian Medicines Agency and the Regional Committee for Medical and Health Research Ethics. One of the three participants who received buprenorphine had pain according to the MOBID-2 (≥ 3). However, we cannot assume that this had influenced the decision to prescribe buprenorphine to this

patient. However, when the violation was discovered, the primary investigator of the study (Bettina Husebo) and my main supervisor (Elisabeth Flo) contacted the University of Bergen, the Norwegian Medicines Agency (SLV) and the Regional Committee for Medical Health Research Ethics (REK). In correspondence with the SLV, Flo and Husebo stated the following: *“The error described above occurred prior to Blytt being employed as a research scholar and commencing her data collection. During her time as a Ph.D. student, Blytt was informed that the study’s exclusion and inclusion criteria were REK and SLV approved. Blytt followed all study procedures conscientiously; procedures that have previously been established in scientific publications and approved by the REK and SLV.”*

The violation could nevertheless have had potentially harmful effects for the patients. As reported by Erdal et al. (2018b), patients who received active buprenorphine had 4.7 times increased risk of discontinuation compared to the placebo group. Patients were excluded because of adverse events, such as agitation, somnolence and nausea. Erdal et al. (2018b) concluded that buprenorphine is poorly tolerated in patients with dementia.

After reviewing the case and the reported data, the SLV concluded as follows (see Appendix 5): *“(…) the Norwegian Medicines Agency is satisfied that both the PI and the ethics committee confirm that the patient safety in the trial has been safeguarded. We do not currently intend to pursue this matter further.”*

The empirical investigations of papers 2 and 3 aimed to provide insight that could improve the sleep of NH patients with dementia. Importantly, the research contribution should exceed the potential burden for patients included in the studies, as discussed in the method chapter. Several patients reacted to the buprenorphine treatment and their reactions were so impactful that we needed to exclude them from the study. As reported by Erdal et al. (2018b), 89 patients were prescribed buprenorphine/placebo transdermal system, of these 44 patients were allocated to

active treatment and 45 to placebo. Compared to six patients in the placebo group, treatment with active buprenorphine transdermal system was discontinued in 23 patients. Nine patients discontinued from the active treatment within the first 14 days compared to two patients in the active treatment. Among those patients who did not tolerate active treatment, approximately half of the patients reported several types of adverse events (Erdal et al. 2018b). The most common cause of adverse events was psychiatric (personality changes, anxiety, agitation, confusion and hallucinations). This implies that for some patients in the study, the burden of taking part may have been excessive. However, the results presented in Erdal et al. (2018b) reflect the effort done by NH staff, Ane Erdal and myself in order to supervise the treatment, and to keep patients safe. In the event that adverse events occurred, patients were quickly withdrawn from the study. However, it should be noted that prior to conducting the study, there was little reason to expect that these negative effects would be widespread. The study design was assessed by the Regional Ethical Committee and the prospective impact on participants was judged as being justifiable.

Doing research in this very fragile and vulnerable group of patients is very important. Becoming old and depending on other people for personal hygiene, care and treatment represent a large challenge for NH patients. Thus, contributing knowledge for better or more evidence-based treatment in this particular group is important, and we believe that despite this violation, the burden on patients has been justifiable.

6.4 A brief comment on the publication strategy

Regarding the publication of the findings in the thesis, it should be noted that the papers 2 and 3 that report sleep-related results from SLEEP.PAIN.DEM were published before the papers reporting the primary outcome of depression (DEP.PAIN.DEM), conducted by Erdal et al. (2018). The reason for this was practical. When the data collection process was finished and data was prepared for analyses in the end of 2016, I had approximately one year left of my PhD period. One

could argue that it would have been ideal to publish the findings for the primary outcome of the DEP.PAIN.DEM trial first. However, those findings were not published until June 2018, while papers 2 and 3 included in this thesis were published already in December 2017 and February 2018, respectively. Thus, due to financial constraints, it would not have been practically feasible to delay the publication of the papers comprised in this thesis until the papers reporting primary outcomes were published. However, the analyses presented in papers 2 and 3 were informed by the ongoing and of preliminary analyses of the primary outcomes (as reported in Erdal et al. 2018a; 2018b).

7. Conclusion

This thesis contributes new and valuable knowledge on sleep in NH patients and the clinical challenges related to sleep in the NH setting.

Paper 1 revealed that sleep disturbances were common in NH patients as measured with actigraphy, but that sleep disturbances were clearly underreported or unrecognised by NH staff when using common clinical tools like the NPI-NH and the CSDD. However, we cannot know if the divergence between the different measurements is due to the raters or the rating instruments. These findings suggest that the clinical usefulness of proxy-rater assessments of sleep is questionable. NH staff should show awareness to potential sleep difficulties among residents in order to identify and potentially treat such challenges.

Paper 2 revealed that short-term pain treatment improved sleep (specifically, SE, SOL and EMA) in NH patients with dementia and depression. For patients with poor sleep at baseline, we found improvement also for TST. Furthermore, patients receiving active buprenorphine transdermal patch had significantly longer TST compared to patients who received active paracetamol. A potential explanation could be sedation, which is a well-known side-effect of opioids.

Paper 3 revealed that pain treatment did not improve sleep in the longer term. Thus, the effects of such treatment found in the short-term did not sustain. However, we found that compared to paracetamol, TST and SE increased among patients who received active buprenorphine transdermal patch treatment. While our results do not yield conclusive evidence upon which novel treatment can be unequivocally recommended, the findings represent a step forward in the understanding of sleep in this vulnerable patient group.

7.1 Clinical implications and future perspectives

In light of the findings from paper 1, the current evaluation of sleep in patients with dementia seems unsatisfactory. However, the financial cost and effort cost of measuring sleep in the NH using actigraphy are arguably excessive. Sleep diaries are an alternative method that could potentially provide valuable information on patients' sleep. The SDI instrument has also shown good correlation with actigraphy, when the population is people with dementia living at home with a caregiver. Future research that further investigates the clinical utility of these tools in the NH would be beneficial. In addition, night-time workers should have a bigger role in evaluating sleep and report issues in a standardised manner.

Although our results show some increase in sleep in the short-term and increase sleep when comparing active buprenorphine and active paracetamol, our research design does not allow us to draw conclusions regarding the underlying mechanism. Future research investigating the relationship between pain, depression and sleep should attempt to include patients with pain, sleep complaints and depression to examine this relationship more thoroughly. Furthermore, it would strengthen the study to include both actigraphy and sleep diaries by proxy as sleep assessment methods.

However, as shown in paper 3, as well as by Erdal et al. (2018a), there was considerable attrition from baseline to week 13 in the group of patients who received active buprenorphine. The findings by Erdal et al. (2018b) are based on a relatively low number of participants, pain was not an inclusion criterion and they are based on secondary data. Still, one should consider whether it would be inappropriate to use buprenorphine in future studies investigating this relationship. It is important to highlight that although paper 2 indicates that sleep as measured with actigraphy increased in the group who received active treatment compared to placebo, and we concluded that pain treatment should be considered to be a potentially beneficial

treatment – we do not recommend pain treatment to improve sleep. When evaluating the results from paper 3 alongside the results from Erdal et al. (2018b), we contend that more research is necessary regarding which opioids might be better tolerated in this vulnerable patient group. This is important to evaluate before new studies investigating the relationship between pain, sleep and depression in people with dementia are conducted.

Systematic assessment of pain, sleep and depression should be part of the everyday routines in the NH, and assessment through self-report could be attempted as part of this effort. This should inform which treatments are considered and followed up with re-assessment after treatment is started. Such assessment would provide information to NH staff regarding how symptoms develop and whether treatment is effective.

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Appendices

Appendix 1: Neuropsychiatric inventory – Nursing Home version – NPI-NH

Appendix 2: Cornell Scale for Depression in Dementia

Appendix 3: Mini Mental Status Examination

Appendix 4: Mobilisation-Observation-Behaviour-Intensity-Dementia-2
Pain Scale

Appendix 5: Statement from the Norwegian Medicines Agency

Appendix 6: Paper 1

Appendix 7: Paper 2

Appendix 8: Paper 3

Appendix 9: Error notice – paper 3

NPI-NH

Variabel	N/A	Hyppighet	Intensitet	Belasting
		0-4	1-3	1-5
1. Vrangforestillinger				
2. Hallusinasjoner				
3. Agitasjon/aggresjon				
4. Depresjon/dysfori				
5. Angst				
6. Oppstemthet/eufori				
7. Apati/likegyldighet				
8. Manglende hemninger				
9. Irritabilitet/labilitet				
10. Avvikende motorisk adferd				
11. Søvn				
12. Appetitt-/spiseforstyrrelser				
			Total	

Hyppighet - hvor ofte skjer adferden?

1. Av og til- sjeldnere enn en gang per uke
2. Ofte - omtrent en gang per uke
3. Hyppig - flere ganger per uke men sjeldnere enn hver dag
4. Svært hyppig - daglig eller oftere

Intensitet – hvor ille er det for pasienten?

1. Mild - medfører liten belastning for beboeren

2. Moderat - forårsaker uvanlig eller merkelig atferd
3. Alvorlig - forstyrrende og forårsaker mye uvanlig eller merkelig atferd.

Belastning – hvor mye merarbeid er det for pleierne?

0. Ikke i det hele tatt

1. Minimalt
2. Mild
3. Moderat
4. Alvorlig
5. Svært alvorlig eller ekstremt

1. Vrangforestillinger

Har beboeren oppfatninger som du vet ikke er riktige? For eksempel, insistere på at folk prøver å skade ham/henne eller stjele fra ham/henne. Har han/hun sagt at familiemedlemmer eller personale ikke er den de utgir seg for å være, eller at ektefellen er utro? Har beboeren hatt andre uvanlige oppfatninger

2. Hallusinasjoner

Har beboeren hallusinasjoner, det vil si ser, hører eller opplever ting som ikke er til stede? (Hvis ja, be om et eksempel for å verifisere at det virkelig er en hallusinasjon). Snakker beboeren til personer som ikke er der?

3. Agitasjon/agresjon

Har beboeren perioder der han/hun motsetter seg hjelp fra andre? Er han/hun vanskelig å ha med å gjøre? Skaper han/hun mye støy eller samarbeider dårlig? Prøver beboeren å skade eller slå andre?

4. Depresjon/dysfori

Virker beboeren trist eller deprimert? Sier han/hun at han/hun føler seg trist eller deprimert? Hender det at beboeren gråter?

5. Angst

Er beboeren svært nervøs, bekymret eller skremt uten noen åpenbar grunn? Virker han/hun veldig anspent eller ute av stand til å slappe av? Er beboeren redd for å være adskilt fra deg eller andre som han/hun stoler på?

6. Oppstemthet/Eufori

Virker beboeren altfor munter eller altfor lykkelig uten spesiell grunn? Jeg mener ikke normal glede, men for eksempel det å le av ting som andre ikke synes er morsomme?

7. Apati/Likegyldighet

Sitter beboeren rolig uten å legge merke til ting som foregår rundt ham/henne? Har han/hun mistet interessen for å gjøre ting eller mangler motivasjon for å delta i aktiviteter? Er det vanskelig å engasjere ham/hun i samtale eller felles aktiviteter?

8. Manglende hemning

Gjør eller sier beboeren ting som man vanligvis ikke gjør eller sier offentlig? Virker det som om han/hun handler impulsivt uten å tenke? Sier beboeren ting som er ufølsomme eller sårende?

9. Irritabilitet/Labilitet

Blir pasienten lett irritert eller urolig? Er humøret hans/hennes svært skiftende? Er han/hun ekstremt utålmodig?

10. Avvikende motorisk atferd

Har beboeren gjentatte handlinger eller "vaner" som han/hun utfører om og om igjen, slik som vandring, kjøre rullestol fram og tilbake, plukke på ting eller tvinne på tråder og snorer? (Ikke inkluder vanlig tremor eller tungebevegelser)

11. Søvn

Har beboeren søvnvansker (symptomet er ikke til stede hvis pasienten må opp på toalettet en eller to ganger om natten for deretter straks å sovne igjen)? Er han/hun våken om nettene? Vandrer han/hun om nettene, kler på seg, eller går inn på andres rom?

12. Appetitt- eller spiseforstyrrelser

Har beboeren hatt en ekstremt god eller dårlig matlyst, vektendring, eller uvanlige spisevaner (skår som NA hvis pasienten ikke er i stand til å spise selv og må mates)? Har det vært noen endring i type mat han/hun foretrekker?

Cornell skala for depresjon – siste uke

Utredningsverktøy til bruk for HELSEPERSONELL OG SYKEHJEMSLEGER

Cornell – skala for depresjon

Alexopoulos et al., 1988. Til norsk Årsland D.

Pasientens navn: _____ Dato for utredning: _____

Utfylt av: _____

Skåringen baseres på symptomer og tegn som har vært til stede siste uke for evalueringen. Skåringen skal ikke baseres på kroppslig funksjonshemming eller sykdom,

NB: Spørsmål nummer 8 og 11 skåres hvis endring har oppstått raskt, for eksempel i løpet av en måned, uansett når, ikke begrenset til siste måned.

Svaralternativ

a. Lar seg ikke evaluere

0. Ikke til stede

1. Moderat eller bare periodevis til stede

2. Mye til stede

a 0 1 2

A: Stemningssymptomer

- | | | | | |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| 1. Angst, engstelig uttrykk, grubling, bekymring | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Tristhet, trist uttrykk, trist stemme, tar til tårene | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Manglende evne til å glede seg over hyggelige hendelser | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Irritabilitet, lett irritert | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

B: Forstyrret atferd

- | | | | | |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| 5. Agitert, rastløs, vrir hendene, river seg i håret | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Retardasjon, langsomme bevegelser, langsam tale, reagerer sent | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Uttalte kroppslige plager (skår 0 hvis bare mage/tarm symptomer) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Tap av interesse, mindre opptatt av vanlige aktiviteter (skår 1 eller 2 bare hvis endringen har skjedd raskt, dvs. i løpet av en måned, ellers 0) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

C: Kroppslige uttrykk

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| 9. Redusert appetitt, spiser mindre enn ellers | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Vekttap (skår 2 hvis større enn 2 kg i løpet av en måned) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Tap av energi, blir fort trett, klarer ikke holde ut aktiviteter (skår 1 eller 2 bare hvis forandringen har oppstått raskt, dvs. i løpet av en måned, ellers 0) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

D: Døgnvariasjoner

- | | | | | |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| 12. Døgnvariasjoner i humør, humør verst om morgenen | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Innsovningsvansker, sovner senere enn det som er vanlig for pasienten | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Hyppige oppvåkninger i løpet av natten | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Tidlig morgenoppvåkning, tidligere enn vanlig for denne pasienten | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

E: Tankeforstyrrelser

- | | | | | |
|--|--------------------------|--------------------------|--------------------------|--------------------------|
| 16. Selvmord, føler livet ikke er verd å leve, har selvmordstanker, gjør selvmordsforsøk | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Dårlig selvbylde, selvbebreidelse, selvnedvurdering, skyldfølelse | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Pessimisme, ser svart på framtiden | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. Vrangforestillinger som samsvarer med å være deprimentert (for eksempel forestillinger om fattigdom, sykdom eller tap) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Cornell sum skåre

MMSE-NR

TL starter med følgende spørsmål: **Synes du hukommelsen har blitt dårligere?** Ja Nei Vet ikke

Jeg skal nå stille deg noen spørsmål, som vi spør alle om. Svar så godt du kan.

Instruksjon kan gjentas, unntatt på oppg. 12 og 17.

TIDSORIENTERING

	Poeng	
1. Hvilket årstall har vi nå? (kun fullt årstall med 4 sifre gir poeng)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
2. Hvilken årstid har vi nå? (ta hensyn til vær og geografiske forhold)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
3. Hvilken måned har vi nå? (kun riktig navn på måned gir poeng)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
4. Hvilken ukedag har vi i dag? (kun riktig navn på dag gir poeng)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
5. Hvilken dato har vi i dag? (kun dagsledd trenger å være riktig for å få poeng)	<input type="checkbox"/> 0	<input type="checkbox"/> 1

STEDSORIENTERING

På spørsmål 7 brukes "Landsdel" ved testing i Oslo, "Fylke" utenfor Oslo.

Sett ring rundt valgt stedsord for spørsmål 8 og 9.

6. Hvilket land er vi i nå?	<input type="checkbox"/> 0	<input type="checkbox"/> 1
7. Hvilket fylke/landsdel er vi i nå? (Sør-Norge gir også poeng for landsdel)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
8. Hvilken by/kommune er vi i nå?	<input type="checkbox"/> 0	<input type="checkbox"/> 1
9. Hva heter dette stedet/bygningen/sykehuset/legekontoret/hvor er vi nå?	<input type="checkbox"/> 0	<input type="checkbox"/> 1
10. I hvilken etasje er vi nå? (Spørsmål stilles også om man er i 1. etasje)	<input type="checkbox"/> 0	<input type="checkbox"/> 1

UMIDDELBAR GJENKALLING/REGISTRERING

Ved retesting: [2. adm: STOL-BANAN-MYNT], [3. adm: SAFT-LAMPE-BÅT], [4. adm: KATT-AVIS-LØK], [5. adm: FLY-EPLER-SKO].

11. **Hør godt etter. Jeg vil si 3 ord som du skal gjenta etter at jeg har sagt dem, og som du skal prøve å huske, for jeg kommer også til å spørre deg om dem senere. Klar? Nå kommer ordene;... HUS [pause], KANIN [pause], TOG [pause]. Nå kan du gjenta disse ordene.**

Dersom pasienten ikke gjentar alle 3 ord, repeteres alle ord inntil alle gjengis i samme forsøk,

maks. 3 presentasjoner. Det gis kun poeng etter 1. presentasjon, rekkefølge pasienten sier

ordene er uten betydning.

Antall presentasjoner: _____stk.

HUS [Ord ved retest:]	<input type="checkbox"/> 0	<input type="checkbox"/> 1
KANIN [Ord ved retest:]	<input type="checkbox"/> 0	<input type="checkbox"/> 1
TOG [Ord ved retest:]	<input type="checkbox"/> 0	<input type="checkbox"/> 1

Husk disse ordene, for jeg vil be deg gjenta dem senere.

OPPMERKSOMHET OG HODEREGNING (Vær oppmerksom på eventuell distraksjonsbetingelse**)

Bruk følgende starttall ved retesting: [2. adm: 50], [3. adm: 90], [4. adm: 40], [5. adm: 60]. Sett ring rundt starttall, skriv ned tallvar. Poeng gis når svar er akkurat 7 fra forrige tall, uavhengig av om forrige tall var riktig.

12. **Kan du trekke 7 fra 80? [Dersom pasienten ikke gir et tallsvar, si: Hva er 80 minus 7?] [Rett etter tallsvar, gis videre instruksjon]: Og så fortsetter du å trekke 7 fra tallet du kommer til, helt til jeg sier stopp [Instruksjon gis kun én gang]. Dersom pasienten heller ikke nå gir et tallsvar, gå videre til distraksjonsbetingelsen**.**

Starttall:	80	50	90	40	60		
	[73]	[43]	[83]	[33]	[53]	_____	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Om nødvendig si: og så videre...	[66]	[36]	[76]	[26]	[46]	_____	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Om nødvendig si: og så videre...	[59]	[29]	[69]	[19]	[39]	_____	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Om nødvendig si: og så videre...	[52]	[22]	[62]	[12]	[32]	_____	<input type="checkbox"/> 0 <input type="checkbox"/> 1
Om nødvendig si: og så videre...	[45]	[15]	[55]	[5]	[25]	_____	<input type="checkbox"/> 0 <input type="checkbox"/> 1

Etter 5 subtraksjoner si: **Fint, det holder** [Gå til oppg. 13].

**Eventuell distraksjonsbetingelse – OBS, er ikke poenggivende!

Dersom pasienten ikke vil utføre eller kan besvare oppg. 12 med 5 avgitte tallsvar, skal distraksjonsbetingelsen brukes for å sikre kartlegging av langtidshukommelse på oppg. 13. Be da pasienten telle baklengs fra 100 ca. 30 sek. med følgende instruksjon: **(Tell baklengs fra 100 på denne måten: 99, 98, 97..., helt til jeg sier stopp. Vær så god!)**

UTSATT GJENKALLING**Poeng**

13. Hvilke 3 ord var det jeg ba deg om å huske? [Ikke gi hjelp/stikkord]

HUS	[Ord ved retest:]	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1
KANIN	[Ord ved retest:]	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1
TOG	[Ord ved retest:]	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1

Nevnes mer enn 3 ord, må pasienten velge hvilke 3 ord som skal være svaret. Rekkefølge er uten betydning. Det gis kun poeng for eksakt gjengivelse, dvs. bolighus, hytte, hare, kanindyr, togbane, lokomotiv etc. gir ikke poeng.

BENEVNING

14. Hva heter dette? [Pek på en blyant] 0 1
15. Hva heter dette? [Pek på et armbåndsur] 0 1

Bruk kun blyant og armbåndsur, gjelder også retesting. Alternative poenggivende svar: Penn, gråblyant, klokke, ur etc.

REPETISJON

16. Gjenta ordrett det jeg sier. Er du klar? [Si tydelig]: "Aldri annet enn om og men" 0 1

TL kan si frasen 3 ganger. Poeng gis kun etter 1. presentasjon. Dialektvariasjoner godtas.

Antall presentasjoner: ____ stk.

FORSTÅELSE

Legg et blankt A4-ark på bordet midt foran pasient, kortsiden mot pasienten. TL legger egen hånd på arket til all instruksjon er gitt. Gi poeng for hver utført delhandling, også dersom pasienten bretter arket med én hånd eller legger arket foran TL.

17. Hør godt etter, for jeg skal be deg gjøre 3 ting i en bestemt rekkefølge. Er du klar? Ta arket med én hånd [pause], brett arket på midten én gang med begge hender samtidig [pause], og gi arket til meg. [pause] Vær så god! [Instruksjon gis kun én gang]

TAR ARKET MED KUN ÉN HÅND	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1
BRETTET ARKET PÅ MIDTEN KUN ÉN GANG	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1
LEGGET ARKET PÅ BORDET FORAN TL ELLER GIR ARKET TIL TL	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1

LESNING

18. Nå vil jeg at du gjør det som står på arket [Vis pasienten teksten].
Pasienten må lukke øynene for poeng.

LUKK ØYNENE DINE	-----	<input type="checkbox"/> 0	<input type="checkbox"/> 1
------------------	-------	----------------------------	----------------------------

SKRIVNING/SETNINGSGENERERING

Legg MMSE-NR skjema side 4 med kortsiden foran pasienten og gi vedkommende en blyant.

19. Skriv en meningsfull setning her [Pek på øvre del av side 4].
Skriver ikke pasienten noe, si: Skriv om været. 0 1

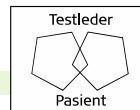
Skrives imperativsetning med kun ett ord, f.eks. "Spis", si: Skriv en lengre setning. Skrives tidligere gitt setning/frase, f.eks. "Lukk øynene dine", "En meningsfull setning", si: Skriv en setning du lager selv.

Setningen må være forståelig, men trenger ikke inneholde objekt. Se eksempler i manual*. Det gis poeng ved riktig utførelse selv etter supplerende instruksjon. Ignorer stave- og grammatikalske feil.

TEGNING/FIGURKOPIERING

Legg figurark over setningen pasienten skrev, viskelær ved siden av.

20. Kopier figuren så nøyaktig du kan her [Pek på nedre del av side 4].
Du kan bruke viskelær. Ta deg god tid. Si fra når du er ferdig. 0 1



Det gis poeng når tegningen består av to 5-kantede figurer som former en 4-sidet figur

der 5-kantene overlapper. Tegnet figur trenger ikke være identisk med modellen. Se skåringseksempler i manual*.

TOTAL POENGSSUM = ____/30. Presiser hva pasienten hadde utfall (feilsvar) på:

Mobid-2 smerteskala

Mobilisation – Observation – Behaviour – Intensity – Dementia

Pasientens navn: _____

Dato: _____ Tid: _____ Avdeling: _____

Vær oppmerksom på pasientens smerteatferd relatert til muskulatur, ledd og skjelett under morgenstell. Observer pasienten før du starter mobilisering. Forklar forståelig det du vil gjøre. Led pasienten, og gjennomfør bevegelsene (1–5) med forsiktighet. Stopp bevegelsen om du observerer smerteatferd. Fyll ut skjemaet umiddelbart etter hver bevegelse.

SMERTEATFERD

Sett ett eller flere kryss for hver observasjon som kan være relatert til smerte; smertelyd, ansiktsuttrykk og avvergeresjon



Smertelyd
«Aul»
Stønner
Ynker seg
Gisper
Skriker



Ansiktsuttrykk
Grimaserer
Rynker pannen
Strammer munnen
Lukker øynene



Avvergeresjon
Støtver
Beskytter seg
Skryter fra seg
Endringer i pusten
Krymper seg

1. Led til å åpne begge hender

2. Led til å strekke armene mot hodet

3. Led til å bøye og strekke anklær, knær og hofteledd

4. Led til å snu seg i sengen til begge sider

5. Led til å sette seg opp på sengekanten

SMERTEINTENSITET

Tolk styrken av smerteintensiteten basert på observert smerteatferd og sett kryss på linjen 0-10, hvor 0 er ingen smerte og 10 er verst tenkelig smerte

0 er ingen smerte, 10 er verst tenkelig smerte

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

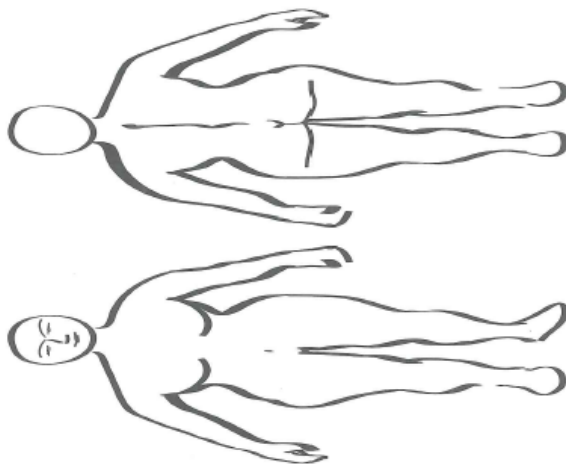
0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

Vær oppmerksom på pasientens smerteatferd relatert til indre organer, hode og hud. Smerte kan oppstå på grunn av en sykdom, sår, infeksjon eller ulykker. Inkluder alle dine observasjoner fra i dag og de siste dagene (siste uken).

SMERTEATFERD

Bruk front- og baksiden av kroppstegningen aktivt. Sett kryss for dine observasjoner relatert til smerteatferd (smertelyder, ansiktsuttrykk og avvergeraksjon)



6. Hode, munn, hals



7. Bryst, lunge, hjerte



8. Mage – øvre del



9. Bekken, mage – nedre del



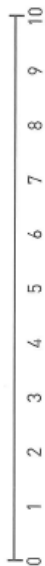
10. Hud, infeksjon, sår



SMERTEINTENSITET

Tolk styrken av smerteintensitet basert på observert smerteatferd og sett kryss på linjen 0–10, hvor 0 er ingen smerte og 10 er verst tenkelig smerte

0 er ingen smerte, 10 er verst tenkelig smerte



Gi en helhetlig vurdering av pasientens smerteintensitet basert på alle observasjoner



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5020 BERGEN
Norge

Exempted from public disclosure cf.
Offl §13 første ledd, jf. fvl. §13 første ledd nr2,
jf. lml. §30

Your ref.:	Date:	Our ref.:	Officer:
Bettina Husebø	9 April 2018	13/10588-21	Maria Almlöf

STATEMENT FROM THE NORWEGIAN MEDICINES AGENCY REGARDING A CLINICAL TRIAL

The Norwegian Medicines Agency (NOMA) has been contacted by Prof. Bettina S. Husebø, who is Principal Investigator (PI) for the DEP.PAIN.DEM trial, EudraCT no. 2013-00226-23. The contact was related to a request for information made by the committee members of Kjersti Marie Blytt's dissertation "Sleep in Nursing Home Patients: Clinical Assessment and the Effects of Pain Treatment on Sleep." Prof. Husebø requested NOMA's comments on identified inconsistencies in the conduct of the clinical trial, the details of which can be found in letter to the committee members dated 2018-03-29. In addition to this letter, the NOMA has also received copies of the attachments (1-4), and the original request from the dissertation committee (dated 2018-03-22).

NOMA has the following comments to the identified issues (please refer to the numbering of the issues as stated in the above mentioned letter of 2018-03-29):

Regarding item 1 – identified discrepancy between NOMA's conditional approval and the allocation of patients who had not previously used pain treatment to the buprenorphine treatment arm:

The inclusion of trial subjects against the approved procedures stated in the protocol is a protocol violation. This is an error which may have serious consequences for the subject safety and/or the robustness of the data generated in a trial. An error of this kind should normally have been detected during routine monitoring of the trial. It is our understanding that the protocol deviation was identified only after the work was published. According to the letter to the committee members, it has been concluded by the concerned ethics committee that the deviation does not have "*discernible serious consequences for the patients*" (quote). NOMA takes note of the standpoint of the ethics committee. Any NOMA conclusion regarding the subject safety or robustness of the data generated in the trial would have to come from a Good Clinical Practice inspection of the trial. It is currently not the intention of the NOMA to perform such an inspection.

Regarding item 2 – we confirm that the approved version of the protocol includes an exclusion criterion for patients who exhibit any contraindication against the use of buprenorphine transdermal patch.

Regarding item 3 – the original submission of the clinical trial application included a version of the protocol which contained the following inclusion criterion related to pain: *“Patients suffering from pain and require continuous treatment with analgesics”*. After a round of correspondence with the NOMA, the pain criterion was removed by the applicant with the following justification: *“We did not intend to make the presence of pain an inclusion criteria, due to the difficulty of assessing pain in patients with dementia, and this point has now been removed from the list of inclusion criteria in section 3 of the revised study protocol.”* The comment to this in the conditional approval letter by the NOMA was: *“the presence of pain has been omitted as inclusion criteria due to difficulties to assess pain in patients with dementia. In light of this we presume that patients without analgesics at enrolment will not be allocated to buprenorphine treatment due to the risk of dependency”*.

Regarding item 4 - No comment.

Conclusion

Although the identified discrepancy between the approved protocol and the included patients is a protocol violation with potential serious consequences for the patients' safety and/or the robustness of the data generated in the clinical trial, the Norwegian Medicines Agency is satisfied that both the PI and the ethics committee confirm that patient safety in the trial has been safeguarded. We do not currently intend to pursue this matter further.

Yours sincerely
Norwegian Medicines Agency

Maria Almlöf
Senior Adviser

This document is electronically approved and sent without signature.

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RESEARCH ARTICLE

Open Access



Clinically significant discrepancies between sleep problems assessed by standard clinical tools and actigraphy

Kjersti Marie Blytt^{1,2,3*} , Bjørn Bjorvatn^{1,3}, Bettina Husebo^{1,2,4} and Elisabeth Flo⁵

Abstract

Background: Sleep disturbances are widespread among nursing home (NH) patients and associated with numerous negative consequences. Identifying and treating them should therefore be of high clinical priority. No prior studies have investigated the degree to which sleep disturbances as detected by actigraphy and by the sleep-related items in the *Cornell Scale for Depression in Dementia (CSDD)* and the *Neuropsychiatric Inventory – Nursing Home version (NPI-NH)* provide comparable results. Such knowledge is highly needed, since both questionnaires are used in clinical settings and studies use the NPI-NH sleep item to measure sleep disturbances. For this reason, insight into their relative (dis)advantages is valuable.

Method: Cross-sectional study of 83 NH patients. Sleep was objectively measured with actigraphy for 7 days, and rated by NH staff with the sleep items in the CSDD and the NPI-NH, and results were compared. McNemar's tests were conducted to investigate whether there were significant differences between the pairs of relevant measures. Cohen's Kappa tests were used to investigate the degree of agreement between the pairs of relevant actigraphy, NPI-NH and CSDD measures. Sensitivity and specificity analyses were conducted for each of the pairs, and receiver operating characteristics (ROC) curves were designed as a plot of the true positive rate against the false positive rate for the diagnostic test.

Results: Proxy-raters reported sleep disturbances in 20.5% of patients assessed with NPI-NH and 18.1% (difficulty falling asleep), 43.4% (multiple awakenings) and 3.6% (early morning awakenings) of patients had sleep disturbances assessed with CSDD. Our results showed significant differences ($p < 0.001$) between actigraphy measures and proxy-rated sleep by the NPI-NH and CSDD. Sensitivity and specificity analyses supported these results.

Conclusions: Compared to actigraphy, proxy-raters clearly underreported NH patients' sleep disturbances as assessed by sleep items in NPI-NH and CSDD. The results suggest that the usefulness of proxy-rater measures of sleep may be questionable and further research is needed into their clinical value. The results highlight the need for NH staff to acquire and act on knowledge about sleep and sleep challenges among NH patients.

Trial registration: Registered at www.clinicaltrials.gov (registration number NCT02238652) on July 7th 2014 (6 months after study initiation).

Keywords: Actigraphy, Proxy-rating, Nursing home, Dementia, Sleep

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Background

In nursing homes (NH), wherein approximately 50–80% of patients have dementia [1–4], sleep disturbances are widespread and severe [5]. Advanced age is associated with a decrease in total sleep time [5], slow-wave sleep and rapid eye movement (REM) sleep [6]. Moreover, approximately 60% experience sleep disturbances at nighttime [7]. Disturbed sleep is associated with multiple negative consequences and predicts an increased risk of developing depression among the elderly [8]. Previous studies have shown that disturbed sleep may lead to reduced quality of life and impaired cognitive daytime functioning in elderly people with and without dementia [9, 10]. As argued by Flo et al. [11], these outcomes may be especially important for the elderly, since such symptoms may be misinterpreted as dementia or more severe dementia. Since so many institutionalized patients are affected by dementia, the consequence may be that they often are no longer able to give valid self-report, a prerequisite for adequate symptom assessment and treatment [12]. Therefore, they depend on the ability of health care professionals to evaluate and treat their distressing symptoms, including sleep disturbances.

Identifying and treating sleep disturbances in this fragile and multimorbid group should be of high clinical priority. However, evaluating sleep in NH patients with dementia is a methodological challenge [13]. Meanwhile, most tools rely primarily on interviewing NH staff members, who function as proxy-raters for the patients. This renders the reliability of such measurement uncertain [14], while their relatively low cost and effort in use, make them attractive in the clinical setting.

Wrist-worn actigraphic recordings are considered the most reliable instrument for objectively measuring sleep in this patient group [15, 16]. However, there is a high cost associated with the use of such equipment. Most et al. [17] compared the subjective assessments tools *Pittsburgh Sleep Quality Index*, *Sleep Disorders Questionnaire*, *Athens Insomnia Scale* and actigraphy. The study showed that the value of sleep questionnaires is limited in early and moderate stage Alzheimer disease and recommended actigraphy as a supplement in detecting sleep disturbances. Meanwhile, Tractenberg et al. [18] showed that scores from the *Sleep Disorders Inventory* (SDI) correlated with actigraphy data, except for 24-h total sleep time and daytime total sleep time. Hoekert et al. [19] similarly found a high degree of correlation between actigraphy and measures in the *Sleep Inventory for Normal and Pathological States*. However, the assessment tools mentioned above are not routinely used in NH settings to assess sleep. Thus, it is of high importance to investigate the accuracy of proxy-rater tools that are commonly used in both the research setting and the clinical setting, and the relative advantages

and disadvantages of actigraphy and proxy-rater tools, respectively.

To our knowledge, no prior studies have investigated the relationship between clinically significant sleep disturbances as detected by actigraphy and by the sleep-related items in the *Cornell Scale for Depression in Dementia* (CSDD) and the *Neuropsychiatric Inventory – Nursing Home version* (NPI-NH), respectively. This is highly needed, since both of the questionnaires are used in clinical settings and several studies use the NPI-NH sleep item to measure sleep disturbances among NH patients [20–23].

Consequently, the aim of this study was to investigate the degree to which actigraphy-based and proxy-rater-based assessments of sleep in NH patients provided comparable clinical outcomes. This allows for an assessment of their relative advantages and disadvantages. The study thus provides insight into similarities and differences in the measurement of sleep disturbances by means of these two approaches, which may provide crucial information for future clinical assessment procedures and research.

Methods

Design and setting of the study

The present study was based on baseline data from the COSMOS trial [24]; a 4-month cluster-randomized and controlled effectiveness-implementation hybrid trial with follow-up at month 9. The study was conducted in Norway from January 2014 to December 2015. To gain a representative distribution of NHs, urban/rural and big/small municipalities were invited. NH patients ≥ 65 years old, with and without dementia, with life expectancy > 6 months, not diagnosed with schizophrenia, were eligible for inclusion. Patients with any form of chronic movement disorder or any form of paralysis in the arms/upper body were excluded from the actigraphy registrations.

Measurements

At baseline, a research team responsible for the COSMOS trial informed and supervised NH staff in the different assessment tools. Only NH staff members who knew the patients were asked to partake in the assessment. Socio-demographic variables were collected from patients' medical records.

Sleep was objectively assessed using the *Actiwatch Spectrum* (*Philips Respironics*). Since NH patients are quite inactive, the actigraphs were placed on the patients' dominant/mobile wrist to increase the possibility of detecting movement. Previous studies have found no difference between data collected from actigraphs placed on different locations [25, 26]. NH staff was instructed to push the event button at bed and rise

times (light off in the night/light on in the morning), both by verbal and written instruction.

We used the following scoring protocols: rest intervals were set using a standardized hierarchical approach based on (1) event markers, (2) light and activity data, and (3) light or activity data. To ensure inter-scoring reliability, 30 of the actigraphy recordings were scored twice by two independent scorers, and compared in terms of total time in bed and total sleep time. To be included, participants would have to complete at least five night recordings. Sleep/wake status was determined for each one-minute epoch using the *Actiware 6 (Respironics)* scoring program and validated algorithm, with the sensitivity set to medium. The scoring was used to generate the following variables: sleep onset latency (SOL), wake after sleep onset (WASO), early morning awakening (EMA), number of wake bouts (NoW),

To define disturbed sleep in this population we followed the quantifiable criteria described in the DSM-5 diagnostic features for insomnia [27]. Hence, we used the following cut-off points to define sleep disturbances as measured with actigraphy: SOL >30 min; WASO >30 min; EMA > 30 min. In addition, we used NoW \geq 3. In accordance with Lacks and Morin [28], we used a cut-off of <85% for sleep efficiency, i.e. time spent asleep divided by time spent in bed [13].

Sleep was subjectively assessed with the NPI-NH, which is a proxy-rater inventory assessing twelve neuropsychiatric symptoms associated with dementia [29]. In the present study, we used item 11 – nighttime behavior – to ascertain sleep disturbances as observed and judged by proxy-raters. Proxy-raters were guided by questions formulated as follows: “Does the patient have sleep problems? Is s/he awake during the night? Does s/he wander during night-time, getting dressed, or going into the room of others?” Each symptom was scored for frequency (score 1–4) and severity (score 1–3), subsequently a product score was calculated thereof. In line with Garcia-Alberca et al. [20] and Chwiszczuk et al. [23], we used a product score \geq 4 as a cut-off to define the presence of sleep disturbances.

Sleep was also assessed by the CSDD, a proxy-rater instrument for the measurement of depression, which is validated both for people with and without dementia [30–32]. Questions regarding sleep fall under the category of “cyclic functions” and comprise item 13 (“Does the patient have difficulty falling asleep?”), item 14 (“Does the patient have multiple awakenings during sleep?”) and item 15 (“Does the patient have early morning awakenings?”). For item 13, a score of 1 was given if the patient only had difficulty falling asleep a few nights in the past week and 2 if there was difficulty every night. For item 14, the patient was given a score of 1 if sleep

was restless and occasionally disturbed. If the patient got out of bed in the middle of the night and/or had woken up every night in the past week, a score of 2 was given. For item 15, a score of 1 was given if the patient woke up early, but then went back to sleep. A score of 2 was given if the patient woke up earlier than usual and could not go back to sleep. A cut-off score of \geq 1 was used to define sleep disturbances identified by proxy-raters for item 13 and 14. For item 15 a cut-off score of 2 was used. Item 13 was used as a measure of problems with SOL, item 14 as a measure of NoW, and item 15 as a measure of EMA, in the comparisons between the CSDD items and actigraphy measurements. The rating is in line with the guidelines by Alexopoulos et al. [30].

Cognitive function was assessed by the *Mini Mental State Examination* (MMSE), which is a 30-point validated scale that consists of 20 tasks. Scores from 0 to 10 indicate severe impairment, 11 to 20 is consistent with moderate impairment, 21 to 25 is consistent with mild impairment, and scores of 26 to 30 suggest no impairment [33, 34].

Statistical analyses

Descriptive statistics were calculated for all relevant variables. McNemar’s tests were conducted to investigate whether or not there were significant differences between the pairs of relevant measures. Cohen’s Kappa tests were used to investigate the degree of agreement between the pairs of relevant actigraphy, NPI-NH and CSDD variables. Sensitivity and specificity analyses were also conducted for each of the pairs of measures. Furthermore, receiver operating characteristics (ROC) curves were calculated, as a plot of the true positive rate against the false positive rate for the diagnostic test. The AUC values of the ROC curves serve to evaluate the performance for each of the pairs of measures. AUC values can be assessed as follows: a value of 1 signifies a perfect test, a value of 0.97 signifies a very good test, values below 0.75 are not considered clinically useful, and values close to 0.5 have no discriminatory value at all [35].

The actigraphy measures were chosen as the reference standard and the analyses measured the degree to which the CSDD and NPI-NH measures captured the same as did the actigraphy measures. To test whether the final actigraphy sample ($n = 83$) differed systematically from the remainder of the study sample ($n = 462$), we conducted independent samples t-tests comparing the mean scores of the two samples for the following variables: age, sex, MMSE score, CSDD scores (difficulty falling asleep; early morning awakening; multiple awakenings) and NPI-NH score (sleep item). We conducted the statistical analyses using *IBM SPSS Statistics 22*.

Ethics

Informed written consent was obtained through direct conversation with patients. If the patient lacked the ability to give consent, we obtained it through direct conversation with the patient's legal guardian. The legal guardian gave presumed consent on behalf of the patient. This is in line with local legislation. The trial was approved by the Regional Committee for Medical and Health Research Ethics, West Norway (REK 2013/1765) and registered at www.clinicaltrials.gov (NCT02238652).

Results

A total of 700 NH patients were invited to participate in the COSMOS study, of which 545 participants from 67 NH units were included. The first 10 patients in every NH unit were evaluated for inclusion in the actigraphy subproject. The actigraphy subproject included 107 patients, 24 of whom were excluded due to actigraph malfunction or because of missing data. The final sample thus included 83 patients who wore actigraphs and had complete CSDD and NPI-NH scores. For the variables outlined above, there were no statistically significant differences between the scores for the actigraphy sample and the remainder of the study sample. Patient characteristics are summarized in Table 1.

Sleep disturbances in NH patients as assessed by actigraphy

The mean number of actigraphy-registered nights per patient was 6.6 (SD = 1.1). Mean time spent in bed was 12 h and 20 min (SD = 1 h 43 min). Mean sleep efficiency was 64.1% (SD = 19.2), and 89.2% of the patients had sleep efficiency <85%. Mean SOL was 57.9 min (SD = 80.1) and 45.8% had SOL >30 min. Mean WASO was 151.8 min (SD = 80.2), i.e. approximately 2.5 h, and 97.6% had WASO >30 min. Mean EMA was 54.5 min (SD = 66.5), and 59.0% of the patients had EMA > 30 min. Mean NoW was 32.1 (SD = 13.4), with a mean length of

Table 1 The table shows descriptive statistics on prevalence (mean values and standard deviations) for socio-demographic variables, NPI-NH¹ sum score = Neuropsychiatric Inventory – Nursing Home version, CSDD² = Cornell Scale for Depression in Dementia. MMSE³ = Mini Mental State Examination. SD = standard deviation

Descriptive statistics (n = 83)	
Age (mean, SD)	86.6 (8.1)
Female (percentage)	75.9% (n = 63)
CSDD ² sum score (mean, SD)	6.0 (5.9)
MMSE ³ sum score (mean, SD)	10.4 (7.5)
MMSE score 20 or below (number, percentage)	59 (86.8%)
MMSE score > 20 (number, percentage)	9 (13.2%)
Number of medications (mean, SD)	7.5 (3.7)

5.1 min (SD = 3.1). All actigraphy results are summarized in Table 2.

Sleep disturbances assessed with NPI-NH compared with actigraphy

Proxy-raters reported sleep disturbances in 20.5% of patients assessed with NPI-NH. McNemar's test comparing sleep efficiency measured with actigraphy and proxy-rater sleep (NPI-NH-SS ≥ 4) showed a significant difference ($p < 0.001$) between the measures (see Table 3). This was supported by the Cohen's Kappa analysis, which showed very low agreement between the measures ($k = .029$).

In the NPI-NH measurements, we found one false positive (i.e. instances where proxy-raters reported sleep disturbances when actigraphy did not) and 57 false negatives (i.e. instances where proxy-raters did not report sleep disturbances when actigraphy did). Compared with the sleep efficiency measure, the sensitivity of the NPI-NH proxy-rater sleep measure was 21.9% (95% CI = 13.4% - 33.4%). The specificity of the measure was 88.9% (95% CI = 50.7% - 99.4%). Thus, the positive likelihood ratio of the test was 1.97, while the negative likelihood ratio of the test was 0.88. The AUC value of the ROC curve was 0.554.

Sleep disturbances assessed with CSDD compared with actigraphy

McNemar's test for actigraphy SOL >30 min (45.8%) and the CSDD "difficulty falling asleep" (18.1%) item showed a significant difference ($p < 0.001$) between the measures

Table 2 Actigraphically measured sleep parameters, mean values with standard deviations

Sleep parameters (n = 83)	
Time spent in bed (hours:min), mean (SD)	12:20 (1:43)
Observation nights, mean (SD)	6.6 (1.0)
Sleep efficiency (%), mean (SD)	64.1 (19.2)
Sleep efficiency below 85%	89.2% (n = 74)
SOL (min), mean (SD)	57.9 (80.1)
Patients with SOL above 30 min	45.8% (n = 38)
WASO (min), mean (SD)	151.8 (80.2)
WASO above 30 min	97.6% (n = 81)
EMA (min), mean (SD)	54.5 (66.5)
EMA above 30 min	59.0% (n = 49)
NoW mean (SD)	32.1 (13.4)
NoW equal or above 3	98.8% (n = 82)
Length of wake bouts (min), mean (SD)	5.1 (3.1)
Bedtime (hours:min), mean (SD)	20:20 (2.21)
Wake up time (hours:min), mean (SD)	8:57 (1:29)

SOL refers to sleep onset latency. WASO refers to wake after sleep onset. EMA refers to early morning awakening. NoW refers to the number of wake bouts

Table 3 Significant differences between actigraphy measured wrist activity compared to percentages of patients' sleep outcome measured with proxy-rated CSDD and NPI-NH

	Actigraphy	CSDD	NPI-NH	<i>p</i>	<i>k</i>
SOL above 30 min or CSDD-DFA ≥ 1	45.8% (<i>n</i> = 38)	18.1% (<i>n</i> = 15)		<0.001	.105
EMA above 30 min or CSDD-EMA ≥ 2	59.0% (<i>n</i> = 49)	3.6% (<i>n</i> = 3)		<0.001	.051
NoW ≥ 3 or CSDD-MA ≥ 1	98.8% (<i>n</i> = 82)	43.4% (<i>n</i> = 36)		<0.001	.019
SE below 85% or NPI-NH-SS ≥ 4	89.2% (<i>n</i> = 74)		20.5% (<i>n</i> = 17)	<0.001	.029

SOL refers to the Sleep Onset Latency measure using actigraphy. EMA refers to the Early Morning Awakening measure. NoW refers to the Number of Wake Bouts measure. SE refers to the Sleep Efficiency measure. CSDD-DFA refers to the Difficulty Falling Asleep measure in the Cornell Scale for Depression in Dementia (CSDD). CSDD-EMA refers to the Early Morning Awakening measure in the CSDD. CSDD-MA refers to the Multiple Awakenings measure in the CSDD. NPI-NH-SS refers to the Subjective Sleep measure in the Neuropsychiatric Inventory – Nursing Home version. *k* = Cohen's Kappa

(see Table 3). This was supported by the Cohen's Kappa analysis, which showed very low agreement between the measures (*k* = .105). In the CSDD SOL measurements, there were six false positives and 29 false negatives. Compared with the actigraphy measure, the sensitivity of the CSDD "difficulty falling asleep" measure was 23.7% (95% CI = 12.0% - 40.6%). The specificity of the CSDD was 86.4% (95% CI = 72.0% - 94.3%). Thus, the positive likelihood ratio of the test was 1.74, while the negative likelihood ratio of the test was 0.88. The AUC value of the ROC curve was 0.550.

McNemar's test comparing EMA > 30 min measured with actigraphy (59%) and the CSDD "does the patient have early morning awakenings?" (EMA) item (3.6%) showed a significant difference (*p* < 0.001) between the measures (see Table 3). This was supported by the Cohen's Kappa analysis, which showed very low agreement between the measures (*k* = .051). In the CSDD EMA measurements, there were no false positives, but 46 false negatives. Compared with the actigraphy measure, the sensitivity of the CSDD EMA measure was 6.1% (95% CI = 1.59% - 17.9%). The specificity of the measure was 100% (95% CI = 87.4% - 100%). Thus, the positive likelihood ratio of the test cannot be calculated, while the negative likelihood ratio of the test was 0.94. The AUC value of the ROC curve was 0.531.

McNemar's test comparing NoW ≥ 3 measured with actigraphy (98.8%) and CSDD "multiple awakenings during sleep" item (43.4%) showed a significant difference (*p* < 0.001) between the measures (see Table 3). This was supported by the Cohen's Kappa analysis, which showed a very low agreement between the measures (*k* = .019). In the CSDD NoW measurements, there were no false positives, but 45 false negatives. Compared with the NoW as measured by actigraphy, the sensitivity of the CSDD "multiple awakenings during sleep" measure was 44.4% (95% CI = 33.5% - 55.9%). The specificity of the measure was not possible to calculate, due to the low number of observations. Thus, the positive likelihood ratio cannot be calculated, but the negative likelihood ratio of the test was 0.56. The AUC value of the ROC curve was 0.722.

Discussion

The aim of this study was to investigate the degree to which actigraphy-based and common proxy-rater-based assessments of sleep in NH patients provided comparable clinical outcomes. This allows for an assessment of their relative merits, when the costs, efforts and benefits of their use are taken into account. Taken together, the analyses (McNemar's test, Cohen's Kappa and sensitivity/specificity analyses, all of which are reported in Table 3) revealed that there were highly significant differences (*p* < 0.001) between the measures with respect to their ability to capture the various sleep outcomes (SOL, EMA and NoW). The Cohen's Kappa values suggested low degrees of agreement between the measures for all pairs of variables. This was also supported by the sensitivity, specificity and likelihood ratio analyses, and the corresponding ROC-curves. The results overall revealed that the CSDD and NPI-NH measures had from very small to small probability for capturing the sleep outcomes detected by actigraphic recordings. This is of key importance since it implies that sleep disturbances may go undetected and thereby untreated among NH patients. These results should be viewed in the context of the nature of the two measures: While actigraphy involves the use of equipment which implies relatively high cost in use, proxy-rater tools are used mostly for screening purposes with low cost and effort.

Using NPI-NH, staff categorized 20.5% of the patients as having sleep disturbances. This was significantly lower than the objective actigraphy measure of sleep, by which 89.2% had sleep efficiency below 85%. Since the study included both patients with and without dementia, it is important to notice that the NPI-NH was developed for use among people with dementia. However, in the total sample, 87% of patients had an MMSE score < 20, which is compatible with dementia [34]. Only 13% had an MMSE score > 20, and the mean MMSE score in this sub-group was 23.6. Based on this, we can assume that most of the patients in the total sample have mild cognitive impairment or dementia. For this reason, we have included the NPI-NH scores of all patients in the present study. Comparing sleep

efficiency with the NPI-NH sleep item is not optimal, since sleep efficiency is a measure of time spent asleep divided by time spent in bed, while the NPI-NH more broadly captures general sleep disturbances. However, sleep efficiency is often used as an indicator of sleep quality [36, 37]. Thus, it can be argued that the sleep item in NPI-NH to some extent should capture sleep quality and/or disturbances. The excessive time in bed reported in our study, which is an important determinant for the calculation of sleep efficiency, is in accordance with previous studies [13, 16].

Actigraphy detected significantly more sleep disturbances relating to SOL, NoW and EMA than did CSDD sleep items. These results thus also indicate that NH staff underreport or do not recognize patients' sleep difficulties, as captured by actigraphy. In contrast, Fetveit and Bjorvatn [13] found that NH staff observations (diaries) of SOL and EMA were consistent with actigraphic recordings. However, the way these parameters are measured is not comparable with the measurements of the present study. NH staff diaries are based on observation during a given period, and the observation is recorded in writing. It is noteworthy, however, that nocturnal awakenings registered by NH staff in the study by Fetveit and Bjorvatn [13] showed little correlation with actigraphy-recorded WASO. This is in line with the present findings, which also indicated that NH staff noticed fewer awakenings compared with actigraphy.

Is the divergence between the actigraphy recordings and proxy-rater assessments due to the raters or due to the rating instruments? A potential reason could be lack of knowledge about sleep among NH staff. This could in turn result in lower perceptiveness in recognizing sleep disturbances. In addition, the proxy-raters were not necessarily night workers. It is possible that observations from night workers were not properly conveyed to the day shift staff. Furthermore, many patients in Norwegian NHs lie in bed during night-time with the cot side of the bed in the upward position. The consequence is that many patients are unable to exit the bed at night. Combined with a reduced capacity for verbal expression due to dementia, this may reduce their interaction with the night shift workers, which could lead to an impression of sleeping even when patients might be awake.

In line with previous research, the results of the present study showed that sleep disturbances are very common among NH patients. Interestingly, the findings indicate that sleep disturbances as measured with actigraphy are even more prevalent now than what was found in earlier studies. Fetveit and Bjorvatn [13] found mean sleep efficiency of 75% among NH patients, with 72% of the patients displaying sleep efficiency below 85%. A pioneering study by Ancoli-Israel *et al.* [38] found that patients on average slept 39.5 min per hour in any hour of the night,

and 50% woke up 2 to 3 times per hour. The patients in the present study displayed a mean sleep efficiency of 64% and as many as 89.2% of the patients had sleep efficiency below 85%.

It is beyond the scope of this study to explore the discrepancy between results regarding actigraphy sleep parameters herein and results from earlier studies. However, a recent report shows that the proportion of NH patients with comprehensive assistance needs has increased from 2009 to 2015. This suggests that the NH population is generally in poorer condition now than earlier [39]. This is notable since previous studies have shown that a decreased ability to sleep is associated with comorbidities [40]. This development may potentially explain some of the discrepancy between prior studies and the present study.

The sample size of 83 patients with actigraphy assessment in the present study is larger than previous studies using actigraphy to assess sleep in this population [13, 16, 41, 42]. The low agreement between actigraphy and proxy-rater measures may simply indicate that the CSDD and the NPI-NH fail to capture sleep difficulties. In light of recent research that indicates that when the CSDD is administered by NH staff, its clinical utility is highly questionable, the discrepancy found in the present study also questions the use of proxy-raters to ascertain symptoms [43]. However, it is noteworthy that we do not recommend actigraphy as the primary tool for evaluating sleep in the NH setting. This would arguably be costly and time consuming, and thus not feasible as a screening tool. However, the results are suggestive of a need for more precise instruments for measuring sleep among NH patients, which could be used in a low-cost and valid manner by proxy-raters.

Limitations

Previous studies indicate that actigraphy is less accurate in distinguishing sleep from wakefulness when sleep efficiency is reduced [22, 35]. Therefore, actigraphy recordings may overestimate sleep relative to sleep diaries and polysomnography [44, 45]. Taking this into consideration, the total amount of sleep may be less and even more fragmented than what is suggested by the results from the present study. This means that the sensitivity for sleep in the NPI-NH and CSDD may be even lower than estimated herein. Meanwhile, polysomnography is not an optimal form for assessing sleep in this patient population. It is difficult to score since electroencephalography does not produce clear patterns of sleep stages in demented patients [15]. Secondly, there is a low tolerance in this group for wearing such equipment [13]. Actigraphy is therefore considered the best method for assessing sleep objectively in this population [15, 16].

Conclusion

The study revealed that when sleep was measured with common clinical tools like NPI-NH and CSDD, sleep disturbances were clearly underreported or unrecognized by NH staff as compared with actigraphy. The results thus suggest that the usefulness of proxy-rater measures of sleep may be questionable and further research is needed into its clinical value. Our results do not allow us to conclude whether the divergence in results are due to the raters or the rating instruments. However, in order to enable NH staff to treat sleep disturbances, the first step is to identify that the patient has a problem. The results therefore highlight the need for NH staff to acquire and act on knowledge about sleep and potential sleep challenges in the population of NH patients, which in turn may increase the likelihood for adequate treatment.

Abbreviations

CSDD: Cornell Scale for Depression in Dementia; EMA: Early morning awakening; MMSE: Mini Mental State Examination; NH: Nursing Home; NoW: Number of wake bouts; NPI-NH: Neuropsychiatric Inventory – Nursing Home version; NPS: Neuropsychiatric symptoms; REM: Rapid eye movement; ROC: Receiver operating characteristics; SDI: Sleep Disorders Inventory; SOL: Sleep onset latency; WASO: Wake after sleep onset

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Availability of data and materials

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Authors' contributions

BH is the primary investigator of the COSMOS trial from which the data originates. KMB designed the study, analyzed the data and wrote the paper. BB, EF and BH designed the study, helped with the analysis of the data and writing of the paper. All authors have read and approved the manuscript prior to publication.

Ethics approval and consent to participate

Informed written consent was obtained through direct conversation with patients. If the patient lacked the ability to give consent, we obtained it through direct conversation with the patient's legal guardian. The legal guardian gave presumed consent on behalf of the patient. The trial was approved by the Regional Committee for Medical and Health Research

Ethics, West Norway (REK 2013/1765) and registered at www.clinicaltrials.gov (NCT02238652).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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RESEARCH ARTICLE

Effects of pain treatment on sleep in nursing home patients with dementia and depression: A multicenter placebo-controlled randomized clinical trial

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Objective: To investigate the effects of pain treatment on sleep in nursing home (NH) patients with dementia and depression.

Methods: A multicenter, 2-armed, double-blinded, placebo-controlled, randomized clinical trial conducted between August 2014 and September 2016. One hundred six long-term patients from 47 NHs in Norway with dementia and depression according to the *Mini-Mental State Examination* and the *Cornell Scale for Depression in Dementia* were included. Patients received stepwise pain treatment in which those who did not use analgesics were randomized to receive either paracetamol (3 g/day) or placebo tablets; those who already used pain treatment were allocated to buprenorphine transdermal system (max. 10 µg/h/7 days) or placebo transdermal patches. Sleep was assessed continuously for 14 days by actigraphy, 1 week of baseline measurement, and 1 week of ongoing treatment. The following sleep parameters were evaluated: total sleep time, sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset, early morning awakening (EMA), and number of wake bouts.

Results: In the intervention group (paracetamol/buprenorphine), SE (70%-72%), SOL (32-24 min), and EMA (50-40 min) improved compared with the control group (SE, 70%-67%; SOL, 47-60 min; EMA, 31-35 min). Treatment effects were significant ($P < .01$, $P < .05$, and $P < .05$, respectively).

Conclusion: Compared with placebo, pain treatment improved sleep as measured with actigraphy. This implies that sleep, pain, and depression in NH patients should be critically evaluated and that pain treatment should be considered to be a potentially beneficial treatment.

KEYWORDS

actigraphy, dementia, depression, nursing home, pain treatment, sleep

1 | INTRODUCTION

Approximately 60% of nursing home (NH) patients experience nighttime sleep disturbances,^{1,2} and 50 to 80% of NH patients have dementia.³⁻⁵ Previous studies have reported that NH patients with dementia have more disturbed nighttime sleep compared with NH patients without dementia.⁶ The capacity to maintain either sleep or wakefulness is further impaired as dementia progresses.⁶ Sleep disturbances among NH patients can be attributed to medical disorders, polypharmacy,⁷ pain,^{8,9}

and depression.^{2,10} Sleep disturbances in this population may have serious consequences, as they increase the risk of falls¹¹ and hip fractures,^{12,13} decrease survival,¹⁴ and impair daytime functioning (eg, reduced memory, concentration, reaction time, and loss of autonomy).¹⁵

Studies indicate that approximately 20 to 30% of NH patients have depression.¹⁶ The close interrelation between pain and depression is often referred to as the pain-depression dyad.¹⁷ This implies that both conditions share common signal pathways and neurotransmitters and that they are responsive to comparable treatments.¹⁷ Depression is also

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associated with sleep disturbances, especially among people with cognitive impairment.^{18,19} Previous research suggests overlapping neural networks for depression, sleep disturbance, and dementia.²⁰ Among various neuropsychiatric symptoms, sleep and depressive symptoms are often considered to coincide as a "mood-cluster."²¹

Pain represents an important cause of poor sleep for people with and without dementia.²² Previous studies indicate that there is a bidirectional relationship between pain and sleep disturbances.²³ Approximately 60% of NH patients experience pain every day.²⁴ The prevalence may vary, however, as pain can be difficult to evaluate in people with dementia, who have reduced ability to describe their symptoms. It is therefore important that NH staff seek to identify pain through appropriate methods²⁵ and exclude pain as a factor contributing to sleep disturbances before prescribing sleep medications. Overall, the presence of pain, dementia, and depression, together with sleep disturbances, may lead to a downward spiral regarding health and well-being.^{15,19}

In a cluster-randomized clinical trial conducted by Husebo et al,²⁶ a stepwise protocol of treating pain was found to improve mood, sleep, and depression in people with dementia and agitation. The study did, however, not include objective sleep measurements and was not placebo-controlled. Consequently, the aim of the present study was to investigate the effect of pain treatment on sleep in NH patients with dementia and depression in a placebo-controlled randomized clinical trial with objective sleep measurements.

We hypothesized that pain treatment would improve total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), waking after sleep onset, early morning awakening (EMA), and number of bouts awake. In addition, we conducted several subgroup analyses. In 1 subgroup analysis, the aim was to investigate the effects of pain treatment on different sleep outcomes for patients with poor sleep at baseline, defined as SE < 85%. In a second analysis, the aim was to investigate if pain treatment improved sleep more in patients who were in pain at baseline, defined as Mobilization-Observation-Behaviour-Intensity-Dementia-2 Pain Scale (MOBID-2) score ≥ 3 . In a final analysis, we aimed to investigate if there were any differences within the active treatment group, ie, between patients receiving active buprenorphine and active placebo, respectively.

2 | METHODS

This study used data collected in the period from 1 week before the intervention until 1 week after the intervention. The study is part of a 13-week, multicenter, parallel-group, double-blind, placebo-controlled randomized trial: "Efficacy of Pain Treatment on Depression in Patients with Dementia—A Randomized Clinical Trial of Efficacy: DEPPAIN.DEM." The study was conducted in Norway from August 2014 to September 2016.

The NHs were located in 11 municipalities in both urban and rural areas and both larger and smaller Norwegian towns. Data collection was conducted by 2 researchers, who recruited NHs through direct contact with NH management. Inclusion and exclusion criteria are listed in Table 1. At the participating NHs, the researchers were granted access to patient medical records to perform prescreening. In cases where no recent (<14 days old) blood analyses (electrolytes,

Key points

- Sleep disturbances are very common among people with dementia.
- Compared with placebo, pain treatment improved sleep in NH patients with dementia and depression, as measured by actigraphy.
- Sleep, pain, and depression in NH patients should be evaluated systematically, and pain treatment should be considered as a potentially beneficial treatment.

hemoglobin, serum creatinine, and serum alanine aminotransferase) were available, new analyses were requisitioned. Patients who were not excluded in the medical record review were screened for depression by using the Cornell Scale for Depression in Dementia (CSDD)²⁷ and for dementia by using the Mini-Mental State Examination (MMSE).²⁸ If the inclusion criteria (CSDD ≥ 8 and MMSE < 20) were fulfilled, the patient was reassessed after written consent had been given. A drop from ≥ 8 to ≥ 6 in CSDD was permitted between screening and baseline. If a patient fulfilled all of the inclusion criteria and none of the exclusion criteria, and inclusion and study treatment were approved by the physician responsible for the patient, the patient was enrolled in the study (see the flow chart in Figure 1 for an overview of enrolment and reasons for exclusion).

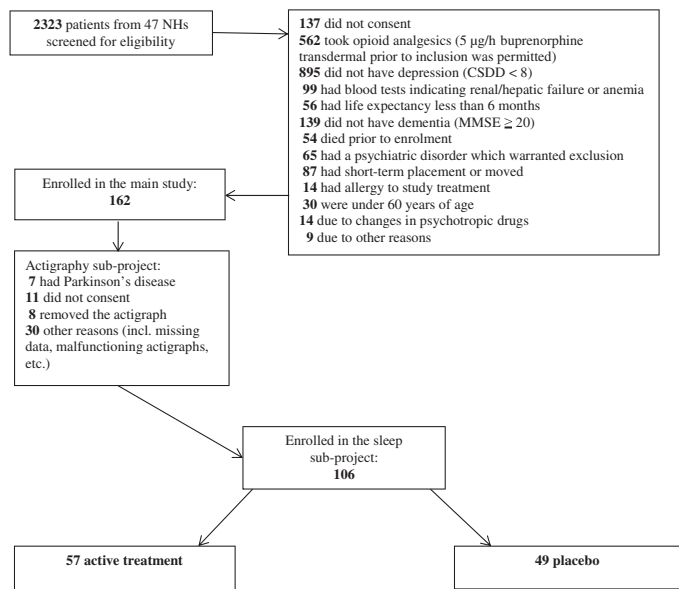
A fixed-dose regimen was used in the study period. The patients were offered a 1-g tablet/placebo at breakfast, lunch, and supper (8 a.m. noon and 6 p.m.). The patients received a stepwise pain treatment, in which those who were taking paracetamol ≤ 1 g/day prior to inclusion were allocated to paracetamol tablets/placebo tablets. The study treatment was prescribed in addition to the basic dose. Patients who were taking nonopioid analgesics/paracetamol >1 g/day, and/or NSAID/buprenorphine, but had difficulty with swallowing tablets were assigned to the buprenorphine/placebo transdermal system. In line with the administrative guidelines, the buprenorphine transdermal patch/placebo patch was changed on a fixed day every week. For patients who were taking buprenorphine transdermal 5 μ g/h prior to inclusion, the study treatment was given as an additional 5- μ g/h transdermal patch (active or placebo). After inclusion, all patients continued their usual medical treatment (including any regular or "as needed" [PRN] analgesic). To ensure stability and control in the study, the clinicians were advised to keep doses of psychotropic and analgesic drugs unchanged during the study period. If any clinical changes occurred, eg, new conditions or injuries, they were to be treated adequately. All withdrawals and reasons were registered.

All sleep-related outcomes were assessed with Actiwatch Spectrum (Philips Respironics). Activity was registered continuously for 14 consecutive days, during which the intervention started on day 8. Data were thus recorded for all sleep parameters for duration of 1 week before and 1 week after the study treatment commenced. The actigraphs were placed on the dominant/mobile wrist. To enable better scoring of the patients' actual time spent in bed, the NH staff were instructed (verbally and written) to register bedtimes and rising times by pushing the event button on the actigraph (light off/lights on).

TABLE 1 Inclusion and exclusion criteria in the actigraphy subproject

Inclusion Criteria	Age \geq 60 years
	Long-term nursing home placement with >4-week stay
	Dementia (MMSE \leq 20)
	Depression (CSDD \geq 8, >3-week duration)
Exclusion criteria	Life expectancy < 6 months
	Severe medical disease that could interfere with study participation
	Severe liver and/or renal impairment
	Anemia (Hb < 8.5 mmol/L) or electrolyte imbalance (Na ⁺ and K ⁺)
	Suicide risk (any attempts during the last year)
	History of severe psychiatric disease prior to dementia onset
	Severe aggression (NPI-NH aggression item score \geq 8, with aggression as the predominant symptom)
	Severe pain (MOBID-2 \geq 7)
	Uncontrolled epilepsy
	Contraindication or clinically significant drug interaction to the assigned study treatment
	Change in psychotropic drugs
	Regular use of any opioid analgesic other than, or exceeding, buprenorphine 5 mcg/h
	Did not want to wear an actigraph
	Immobile patients (paralysis, or otherwise bedridden)
	Patients with involuntary movement (eg, Parkinson disease)
	Less than 5 nights of actigraphy recordings

Abbreviations: CSDD indicates Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilization-Observation-Behaviour-Intensity-Dementia-2 Pain Scale; NPI-NH, Neuropsychiatric Inventory-Nursing Home Version.

**FIGURE 1** Flow chart screening and inclusion

The Actiware 6 (Respironics) was used for sleep scoring. Sensitivity was set to medium, and sleep/waking status was determined for each 1-minute epoch. A trained technician scored all the activity protocols. A standardized hierarchical approach was used to set rest intervals for the actigraphy data, using (1) event markers when possible, or (2) light and activity data, or (3) light or activity data. Alternatives 2 and

3 were only implemented if there was a clear differentiation between active and rest periods; if not, the actigraphy protocol was excluded.

Depression was assessed by using the validated CSDD. The CSDD consists of 19 items measuring 5 domains of depression (mood, behavioral disturbances, physical signs, cyclic functions, and ideational disturbances). A cut-off point of 8/9 has demonstrated the best accuracy for

diagnosing depression according to the International Statistical Classification of Diseases and Related Health Problems 10th Edition criteria.²⁷ The assessment was conducted by using only information provided by NH staff members who knew the resident very well.

Pain was assessed by the MOBID-2, a validated staff-administered instrument for measuring pain in people with advanced dementia.²⁵ The instrument provides a total score based on all of the observations ranging from 0 to 10, where 10 represents the worst possible pain.²⁵ A score of ≥ 3 has been used as a cut-off to indicate clinically relevant pain.²⁵

Cognitive function was assessed by using the validated MMSE.²⁸ The MMSE is a brief, cognitive screening test with a 30-point scale that consists of 20 tasks and was developed to distinguish potential dementia from normal functioning.²⁹ Five patients started the MMSE screening and scored very poorly and subsequently withdrew from the MMSE screening. This led to missing data. For these patients, cognitive function was assessed by proxy through conversations with primary doctors and nurses as an alternative to MMSE screening.

The patients were randomly allocated to each arm in a 1:1 ratio, using computer-generated random numbers. The randomization list was produced by a statistician, without any involvement of the research team. There was no use of stratification factors. The research team was provided with a blinded, sequential list of pack identification numbers, and the patients were consecutively assigned to the next pack number in the list upon inclusion. The study was double-blinded, and all researchers, patients, and NH staff were masked regarding the group allocation.

Descriptive statistics were calculated for all relevant variables. Comparisons of sleep parameters pre- and posttreatments were performed as a mixed within-between subjects ANOVA (placebo versus active treatment and pretreatment versus posttreatment). Differences between pre- and posttreatments within each treatment group were assessed with paired *t* tests for each of the experimental groups separately. Furthermore, we conducted additional 2×2 mixed within-between subjects ANOVA analyses. One of these analyses investigated patients who had sleep disturbances at baseline, defined as $SE < 85\%$,³⁰ and compared the effect of active and placebo

treatments for those patients. A second analysis compared the effect of the treatments for a subgroup of patients whose MOBID-2 score was ≥ 3 , ie, patients who had pain at baseline. The last analysis investigated patients in the active treatment group and thus compared the effect of active buprenorphine to that of active paracetamol. The statistical analyses were conducted by using IBM SPSS Statistics 22.

Each patient's medical decision-making capacity was discussed with the patient's primary nurse at the NH. Attempts were made to adjust the information for patients who had reduced capacity to give consent (MMSE score from 16 to 19).³¹ In addition, the researchers contacted all of the eligible patients' legal guardians. If the legal guardians gave presumed consent on behalf of the patient, they received written and oral information together with a consent form that they signed and mailed back. The study was approved by the Regional Ethics Committee (REC-West 2013/1474). The study's clinical trial number is NCT02267057.

3 | RESULTS

In total, 2323 patients were screened for eligibility, of whom 162 were eligible to participate as part of the broader study. The final sample of the actigraphy subproject included 106 participants (see Figure 1). Of the 106 patients, 49 were randomly assigned to the placebo group and 57 to the active treatment group. In the active treatment group, 2 patients dropped out due to their reaction to the treatment. In the total sample of patients with actigraphs, the mean age was 85.5 years ($SD = 7.3$), 76% were female, the mean CSDD score was 11.2 ($SD = 3.7$), the mean MMSE score was 7.6 ($SD = 6.0$), the mean MOBID-2 score was 2.8 ($SD = 2.1$), and 54.7% had a MOBID-2 score ≥ 3 . Sleep characteristics pre- and posttreatments for patients in both experimental groups, as well as the interaction effect for each sleep outcome, are shown in Table 2.

In the total sample ($n = 106$), SE, SOL, and EMA all improved for the active treatment group compared with the placebo group (see Table 2). The analysis of the treatment for the subgroup of patients with preexisting sleep disturbances ($SE < 85\%$) identified at baseline

TABLE 2 Within- and between-group effects of the placebo and active treatments on different sleep outcomes

	Placebo Group (n = 49)			Active Group (n = 55)			Interaction Effect ^c	
	Mean (SD) Pre ^a -Post ^a **	P Value ^a	Effect Size ^b	Mean (SD) Pre ^a -Post ^a **	P Value ^a	Effect Size ^b	F value	P Value
TST (min)	509.9 (113.6)-498.8 (126.5)	.164	0.20	515.6 (136.7)-526.9 (119.7)	.235	0.16	3.25	.074
SE (%)	70.0 (13.1)-67.5 (14.8)	.036	0.31	69.9 (14.8)-72.2 (12.5)	.039	0.29	9.11	.003
SOL (min)	47.0 (44.5)-59.6 (80.3)	.187	0.19	31.7 (35.2)-24.6 (28.2)	.079	0.24	4.03	.047
WASO (min)	140.6 (68.3)-143.3 (68.3)	.610	0.07	136.0 (66.7)-134.5 (58.2)	.800	0.03	0.27	.604
EMA (min)	30.7 (38.9)-35.2 (35.5)	.268	0.16	50.1 (61.1)-40.5 (37.5)	.082	0.24	4.20	.043
NoW (no.)	31.2 (11.6)-30.3 (11.8)	.404	0.12	30.0 (11.9)-29.4 (13.5)	.551	0.08	0.05	.831

Notes: TST indicates total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, waking after sleep onset; EMA, early morning awakening; NoW, number of bouts awake.

^aPaired *t* test, comparing values before and after the intervention (separate tests for the placebo group and the active group).

^bEffect size (Cohen's *d*) for paired values.

^cA mixed within-between subjects 2×2 ANOVA comparing the placebo and active treatments.

^aPre = -7 to 0 days (baseline).

^aPost = 1 to 7 days active/placebo treatment.

TABLE 3 Effects of the placebo and active treatments on different sleep outcomes for patients with SE < 85%

	Group With SE Below 85% (n = 89)								
	Placebo Group (n = 44)			Active Group (n = 45)			Interaction Effect ^c		
	Mean (SD) Pre*-Post**	P Value ^a	Effect Size ^b	Mean (SD) Pre*-Post**	P Value ^a	Effect Size ^b	F Value	P Value	
TST (min)	488.8 (97.6)-475.3 (108.1)	.107	0.25	477.7 (114.6)-497.6 (103.9)	.065	0.28	6.25	.014	
SE (%)	67.5 (11.3)-64.9 (13.3)	.049	0.30	65.4 (12.4)-69.0 (10.8)	.005	0.44	12.18	.001	
SOL (min)	51.9 (44.4)-66.0 (82.4)	.182	0.20	37.3 (36.5)-28.2 (29.7)	.063	0.28	4.17	.044	
WASO (min)	150.7 (63.9)-153.5 (63.5)	.635	0.07	154.4 (58.3)-148.7 (50.3)	.432	0.12	0.83	.363	
EMA (min)	33.7 (40.0)-37.2 (36.3)	.418	0.12	58.5 (64.5)-45.6 (39.1)	.049	0.30	4.51	.036	
NoW (no.)	31.7 (11.6)-30.5 (11.4)	.339	0.15	32.5 (10.6)-31.5 (12.3)	.365	0.14	0.00	.957	

Notes: TST indicates total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, waking after sleep onset; EMA, early morning awakening; NoW, number of bouts awake.

^aPaired t test, comparing values before and after the intervention (separate tests for the placebo group and the active group).

^bEffect size (Cohen's *d*) for paired values.

^cA mixed within-between subjects 2 × 2 ANOVA comparing the buprenorphine and paracetamol groups for the patients with poor sleep efficiency.

*Pre = -7 to 0 days (baseline).

**Post = 1 to 7 days active/placebo treatment.

TABLE 4 Effects of the placebo and active treatments on different sleep outcomes for patients with pain (MOBID-2 ≥ 3) at baseline

	Group With Pain (n = 46)								
	Placebo Group (n = 25)			Active Group (n = 21)			Interaction Effect ^c		
	Mean (SD) Pre*-Post**	P Value ^a	Effect Size ^b	Mean (SD) Pre*-Post**	P Value ^a	Effect Size ^b	F Value	P Value	
TST (min)	518.3 (126.0)-523.8 (130.7)	.528	0.13	554.4 (141.8)-565.2 (127.8)	.223	0.27	0.18	.667	
SE (%)	70.3 (14.9)-69.4 (14.4)	.330	0.20	74.1 (14.5)-75.7 (13.6)	.122	0.35	3.56	.066	
SOL (min)	42.5 (44.7)-49.5 (66.9)	.413	0.17	25.1 (26.5)-23.0 (24.9)	.611	0.11	0.84	.362	
WASO (min)	137.7 (67.1)-140.4 (75.0)	.737	0.07	128.2 (73.5)-124.7 (70.4)	.683	0.09	0.28	.595	
EMA (min)	37.3 (51.4)-36.7 (39.7)	.906	0.02	34.0 (36.4)-29.9 (30.2)	.276	0.24	0.34	.559	
NoW (no.)	31.3 (12.7)-30.1 (13.3)	.407	0.17	29.7 (14.2)-30.5 (15.6)	.623	0.11	0.88	.351	

Notes: TST indicates total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, waking after sleep onset; EMA, early morning awakening; NoW, number of bouts awake.

^aPaired t test, comparing values before and after the intervention (separate tests for the placebo group and the active group).

^bEffect size (Cohen's *d*) for paired values.

^cA mixed within-between subjects 2 × 2 ANOVA comparing the placebo and active treatments for the patients with pain (MOBID-2 score ≥ 3).

*Pre = -7 to 0 days (baseline).

**Post = 1 to 7 days active/placebo treatment.

TABLE 5 Effects of the placebo and active treatments on different sleep outcomes for patients given active buprenorphine and paracetamol

	Group With Active Treatment (n = 55)								
	Paracetamol Group (n = 25)			Buprenorphine Group (n = 30)			Interaction Effect ^c		
	Mean (SD) Pre*-Post**	P Value ^a	Effect Size ^b	Mean (SD) Pre*-Post**	P Value ^a	Effect Size ^b	F Value	P Value	
TST (min)	531.5 (145.5)-518.3 (131.4)	.233	0.24	502.3 (129.9)-534.0 (110.9)	.029	0.42	6.176	.016	
SE (%)	72.2 (14.1)-72.4 (12.7)	.854	0.04	68.0 (15.4)-72.1 (12.6)	.027	0.42	3.252	.077	
SOL (min)	34.0 (35.5)-29.0 (33.5)	.238	0.24	29.8 (35.4)-20.9 (22.8)	.181	0.25	0.241	.626	
WASO (min)	121.3 (63.8)-123.6 (52.8)	.762	0.06	148.3 (67.7)-143.5 (61.7)	.610	0.09	0.333	.566	
EMA (min)	42.9 (47.4)-39.7 (39.7)	.562	0.12	56.1 (70.8)-41.2 (36.2)	.101	0.31	1.173	.284	
NoW (no.)	28.5 (11.8)-28.4 (13.6)	.969	0.01	31.3 (12.1)-30.2 (13.6)	.464	0.14	0.244	.624	

Notes: TST indicates total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, waking after sleep onset; EMA, early morning awakening; NoW, number of bouts awake.

^aPaired t test, comparing values before and after the intervention (separate tests for the buprenorphine group and the paracetamol group).

^bEffect size (Cohen's *d*) for paired values.

^cA mixed within-between subjects 2 × 2 ANOVA comparing the buprenorphine and paracetamol groups for the patients who received active treatment.

*Pre = -7 to 0 days (baseline).

**Post = 1 to 7 days active/placebo treatment.

($n = 89$) confirmed the main effects (see Table 3). In addition, TST improved significantly for the active treatment group compared with the placebo group (see Table 3). Interestingly, when analyzing the effect of treatment for the subgroup of patients who experienced pain at baseline ($n = 46$), we found no significant differences between active and placebo treatment for any of the sleep outcomes (see Table 4). In a final analysis, we investigated if there were any differences within the active treatment group (see Table 5). We found a significant increase in TST for patients who received active buprenorphine compared with those who received active paracetamol (see Table 5).

4 | DISCUSSION

The results of the present study gave partial support to our hypotheses. The study demonstrated that active pain treatment for people with dementia and depression improved 3 central sleep parameters: SE, SOL, and EMA. When we analyzed the subgroup with poor sleep at baseline, the results were further strengthened, with an additional improvement in TST. Moreover, the group of patients who received the active buprenorphine transdermal patch had significantly longer TST compared with the active paracetamol group. However, being in pain at baseline was not associated with improved sleep after active treatment.

To the best of our knowledge, this is the first placebo-controlled randomized clinical trial to investigate the efficacy of pain treatment on sleep among NH patients with dementia and depression. The study is of key importance for clinicians, because it provides new insight into the complex and poorly understood relationship among pain, depression, and sleep. There is a great need for such insight, because sleep disturbances are endemic among NH patients, and knowledge regarding potential treatment is essential.

Even though the underlying mechanisms of the results are unknown and the clinical value of the treatment effect is uncertain, the results indicate that pain treatment may contribute to improved sleep among some NH patients with dementia and depression. As described above, there were patients already receiving pain medication (paracetamol) prior to inclusion. However, our results suggest that some of the patients might not be adequately treated, with paracetamol alone or only with a low dose. Therefore, these patients may experience beneficial effects of stronger medication (eg, buprenorphine) or an increased dose of already prescribed medication.

Interestingly, when we conducted subgroup analyses of the patients with sleep disturbances (defined as $SE < 85\%$), we found significant improvement in TST in addition to SE, SOL, and EMA, indicating that the group of patients with poor sleep might derive greater benefit from pain treatment. Husebo et al³² found that a systematic approach to pain management significantly reduced agitation among people with dementia and agitation. In a different study, also conducted by Husebo et al,²⁶ the results showed that mood symptoms, including depression and sleep disturbances, improved with pain treatment in the same patient group. This was partly attributed to potentially untreated pain.^{26,32} Interestingly, in the present study, we found no improvements in sleep in the subgroup of patients in pain at baseline. Thus, the results do not support that the underlying

mechanism is untreated pain. It should be noted that the subgroup analysis only included 21 patients with active treatment and pain according to MOBID-2. The lack of significant differences could therefore be due to the low sample size. It is noteworthy, however, that Zancocci et al³³ found no association between sleep problems and the presence of pain, although pain intensity was associated with patients' sleep disturbances.

Furthermore, the results showed that TST increased significantly among patients who received active buprenorphine compared with patients who received active paracetamol. Because sedation is a frequently reported opioid-associated side effect, which is more likely to occur at the onset of therapy or with dose increase,³⁴ this may suggest an opioid-associated sedation effect. Actigraphy only records movement, and a total lack of movement would therefore be assessed as sleep. It is not possible to examine the question of whether there is a sedation effect further with this study design.

In the present study, the NH patients wore the actigraph on the dominant or mobile wrist. This choice was made because many NH patients have limited mobility, due to medical conditions (eg, stroke or paralysis) or general fragility and inactivity. Therefore, potential activity would more likely to occur first in the dominant or mobile wrist. This implies that wearing the actigraph on the dominant wrist increases the probability of activity to be registered. There are no standards regarding the placement (dominant/nondominant wrist) of the actigraph.³⁵ However, in prior studies on persons with dementia, the dominant wrist is most commonly used. For instance, Camargos et al³⁵ recommended using the dominant or mobile wrist. It would, however, be valuable to assess the potential differences between measurements on the nondominant versus the dominant wrist in future research.

The results should be interpreted with caution because the study design does not allow us to assess if the improvement is of subjective value for the patient. Further research is necessary to investigate this more extensively. However, the results of this study suggest that clinicians should evaluate pain, sleep, and depression by using proper assessment tools and, based on such evaluation, consider pain treatment as potentially beneficial for patients with sleep disturbances.

5 | LIMITATIONS

Our study has some limitations. The use of multiple sleep-related outcome measures is a potential study limitation, which can potentially lead to type I errors. We do not correct for multiple comparisons in our study. However, a simple Bonferroni correction would be overly conservative and would increase the risk of type II errors.³⁶ Therefore, we urge the reader to take the lack of such correction into account in the interpretation of the findings of the study.

In actigraphy recordings, immobility of the participants marks the beginning of the sleep period. Sleep onset latency has been particularly difficult to ascertain with actigraphy, because patients may just be lying still in bed and it can be recorded as sleep.³⁷ In addition, previous studies show that actigraphy is less precise in differentiating between sleep and wakefulness when SE is reduced.³⁷⁻³⁹ Both of these factors may lead to an overestimation of sleep.

The comprehensive combination of inclusion and exclusion criteria made it difficult to recruit patients to the study. Of the 2323 patients screened for potential eligibility, a total of 895 did not have depression according to CSDD. In addition, there has been a change in the prescription of pain medication for NH patients during the last decade that influenced inclusion. Sandvik et al⁴⁰ found that analgesic drug prescription at NHs increased significantly from 2000 to 2011, and in particular the use of paracetamol and strong opioids. This impeded the inclusion of patients in the study, as a high number of patients were already taking high doses of opioids (n = 562) and could not be included. This may have excluded some people with depression or sleep problems, who could have benefited from the study intervention. This renders the generalizability of our study questionable because our sample may not be representative for the general NH population.

Furthermore, the subgroup analysis is based on a low number of respondents, which implies that we cannot exclude type 2 errors. Another central limitation in the study is that it does not include pain assessment during the week after the intervention. As a consequence, we do not know how pain progressed after the intervention. Future research should include a larger sample of patients with pain at baseline to account for a large attrition rate and follow-up with pain assessments after the intervention is given. A further limitation of our study was that we did not conduct a priori power analyses, which would have been beneficial for assessing if the statistical tests have sufficient power. However, our sample is similar to or larger than samples in comparable studies. The reader should, however, interpret the findings with caution, in particular for the subgroup analyses with lower sample sizes.

6 | CONCLUSION

Compared with placebo, pain treatment improved actigraphy-measured sleep in NH patients with dementia and depression. This implies that sleep, pain, and depression in NH patients should be evaluated critically and that pain treatment should be considered as a potentially beneficial treatment for residents with poor sleep. Future research should focus on the underlying mechanisms and explore the subjective value of such treatment for the NH patient.

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CONFLICT OF INTEREST

Mundipharma International supplied the study medication, but the company did not influence the study design, data collection, analyses and interpretation of data, or final publication.

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Long-Term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-Week Randomized Placebo-Controlled Trial

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Objective: Previous research indicates that pain treatment may improve sleep among nursing home patients. We aimed to investigate the long-term effect of pain treatment on 24-h sleep patterns in patients with comorbid depression and dementia.

Design: A 13-week, multicenter, parallel-group, double-blind, placebo-controlled randomized clinical trial conducted between August 2014 and September 2016.

Setting: Long-term patients from 47 nursing homes in Norway.

Participants: We included 106 patients with comorbid dementia and depression according to the *Mini Mental Status Examination (MMSE)* and the *Cornell Scale for Depression in Dementia (CSDD)*.

Intervention: Patients who were not using analgesics were randomized to receive either paracetamol (3 g/day) or placebo tablets. Those who already received pain treatment were randomized to buprenorphine transdermal system (maximum 10 µg/h/7 days) or placebo transdermal patches.

Measurements: Sleep was assessed continuously for 7 days by actigraphy, at baseline and in week 13. Total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO), early morning awakening (EMA), and number of wake bouts (NoW) were evaluated. In addition, daytime total sleep time (DTS) was estimated. Pain was assessed with *Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale (MOBID-2)*.

Results: The linear mixed model analyses for TST, SE, SOL, WASO, EMA, NoW and DTS showed no statistically significant differences between patients who received active pain treatment and those who received placebo. *Post hoc* subgroup analyses showed that there were no statistically significant differences between active treatment and placebo from baseline to week 13 in patients who were in pain (MOBID-2 ≥ 3) at

baseline, or in patients who had poor sleep (defined as SE < 85%) at baseline. Patients who received active buprenorphine showed an increase in TST and SE compared to those who received active paracetamol.

Conclusion: The main analyses showed that long-term pain treatment did not improve sleep as measured with actigraphy. Compared to paracetamol, TST and SE increased among patients who received buprenorphine. This could indicate that some patients had beneficial effects from the most potent pain treatment. However, based on the present findings, long-term pain treatment is not recommended as a strategy to improve sleep. Clinical Trial <https://clinicaltrials.gov/ct2/show/NCT02267057>.

Keywords: sleep, nursing home, actigraphy, pain treatment, depression, pain

INTRODUCTION

Approximately 46.8 million people worldwide suffer from dementia – a number estimated to reach 131.5 million by 2050 (Prince et al., 2016). In nursing homes (NH), 50–80% of patients have dementia (Helvik et al., 2015; Blytt et al., 2017b), a neurodegenerative condition that results in the decline of physical and cognitive functions (Cricco et al., 2001). Sleep disturbances are common among NH patients with dementia, with prevalence ranging from 24.5% (Moran et al., 2005) to 60% (Neikrug and Ancoli-Israel, 2010; Ownby et al., 2014; Peter-Derex et al., 2015). Dementia may induce pathophysiological changes in the brain, which can interfere with the maintenance of normal sleep (Moran et al., 2005; Neikrug and Ancoli-Israel, 2010). Previous studies have reported that people with dementia have more disturbed sleep than do patients without dementia (Pat-Horenczyk et al., 1998). It is further noteworthy that previous research indicates that NH patients with dementia are rarely asleep or awake for a full hour in the 24-h cycle (Jacobs et al., 1989). NH patients may suffer dramatic consequences from sleep disturbances, for instance by increasing the risk of falls and hip fractures (Stone et al., 2004; Morley, 2013; Widera, 2013) and decreasing survival (Dew et al., 2003). Furthermore, sleep disturbances contribute to impaired daytime functioning (Cricco et al., 2001).

Several factors contribute to sleep disturbances among NH patients, including pain (Chen et al., 2011; Flo et al., 2017) and depression (Giron et al., 2002). Approximately 20–30% of NH patients have depression, a disorder highly associated with sleep disturbances (Potter and Steffens, 2007). Depression is a common mental disorder, of which central symptoms are low mood and low or loss of ability to experience pleasure (American Psychiatric Association, 2013). Around 50% of the people with Alzheimer disease experience depression during the course of the disease (Lyketsos and Olin, 2002). Furthermore, nearly 60% of NH patients experience pain every day (Husebo et al., 2010). Pain is an unpleasant sensory and emotional experience (Onen et al., 2005) and represents an important cause for poor sleep among NH patients (Morley, 2013). Patients with dementia may have reduced capacity to express symptoms, e.g., pain or sleep disturbances. For this reason, it is essential that NH staff strives to evaluate symptoms through appropriate methods. Research suggests that pain and depression share common signal

pathways and neurotransmitters, which implies that they may be responsive to comparable treatments. This intimate relationship is denoted the pain-depression dyad (Chopra and Arora, 2014).

Medications such as atypical antipsychotics, benzodiazepines and other GABAergic drugs are often sought to alleviate sleep problems in people with dementia (McCleery et al., 2016). However, previously conducted studies indicate that the source of sleep problems might be changes in the brain caused by dementia (Montplaisir et al., 1995, 1998; Kinnunen et al., 2017). Therefore, the efficacy of treatment with various drugs in this patient group is highly questionable (McCleery et al., 2016). Meanwhile, a study conducted by Husebo et al. (2013) found that a stepwise protocol for treating pain improved mood and sleep, as measured with the *Neuropsychiatric Inventory – Nursing Home version (NPI-NH)*, in people with advanced dementia and agitation. Furthermore, in a recently published randomized controlled trial, based on the same dataset and respondents as the present work, we found that compared to placebo, pain treatment improved sleep after 1 week of treatment (Blytt et al., 2017a). In the present study, we aim to investigate the long-term effect of pain treatment on sleep in patients with comorbid dementia and depression. In light of the results from Blytt et al. (2017a), we hypothesized that long-term pain treatment would improve sleep after 13 weeks in patients with comorbid dementia and depression.

In additional *post hoc* subgroup analyses, we further aimed to investigate if improvement of sleep from pain treatment was larger in patients who were in pain at baseline, defined as *Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale (MOBID-2)* score ≥ 3 , than in those who were not. In addition, we aimed to investigate the effects of pain treatment on different sleep outcomes for patients with poor sleep at baseline, defined as sleep efficiency (SE) < 85%. In the last analysis, we aimed to examine if there were any differences within the active treatment group, i.e., between patients receiving active buprenorphine and active placebo, respectively.

MATERIALS AND METHODS

The study is based on an actigraphy subproject in the 13-week, multicentre, parallel-group, double-blind, placebo-controlled randomized trial “*Efficacy of Pain Treatment on Depression in*

Patients with Dementia – A Randomized Clinical Trial of Efficacy: DEP.PAIN.DEM. The study was conducted from August 2014 to September 2016, in Norway. We included 47 NHs from 11 municipalities, located in both urban and rural areas in Norway. In the present study, we used sleep data collected in the week before treatment commenced (baseline) and in week 13 of the treatment/placebo period.

Participants and Procedures

Data collection was led by two researchers who enrolled NHs through direct contact with NH management. If the management agreed to be part of the project, the researchers were given access to patient medical journals to perform a pre-screening review. If there were no recent blood analyses (electrolytes, hemoglobin, serum creatinine, and serum alanine aminotransferase) available, new were requisitioned. In order to be included, patients had to be ≥60 years, long term NH patients with >4 weeks of stay, dementia as indicated by *Mini Mental State Examination* (MMSE ≤ 20) and depression as indicated by the *Cornell Scale for Depression in Dementia* (CSDD ≥ 8). Patients were excluded from the study if they had severe medical disease that

could interfere with study participation, were using any opioid analgesic (except buprenorphine 5 mcg/h), did not want to wear an actigraph, were immobile or had involuntary movements. Inclusion and exclusion criteria are covered extensively in Blytt et al. (2017a). The patient was reassessed after written consent was given, and a drop from ≥8 to ≥6 in CSDD was permitted between screening and baseline. In addition to all of the inclusion and exclusion criteria, the treatment needed to be approved by the physician responsible for the patient (see the flow chart in **Figure 1** for an overview of enrolment and reasons for exclusion). We assessed the patients with the same measurements at baseline and in week 13 of the treatment period.

A stepwise protocol, with a fixed-dose regimen, for treating pain was used in the study period (see **Table 1**). Patients were allocated either to a paracetamol group or to a buprenorphine group and randomized to receive active treatment or placebo. If a patient showed any signs of not tolerating the treatment (e.g., headache, dizziness or nausea), needed to change medical treatment, or there was anything else conflicting with the patient taking part in the study, the patient was withdrawn from the study

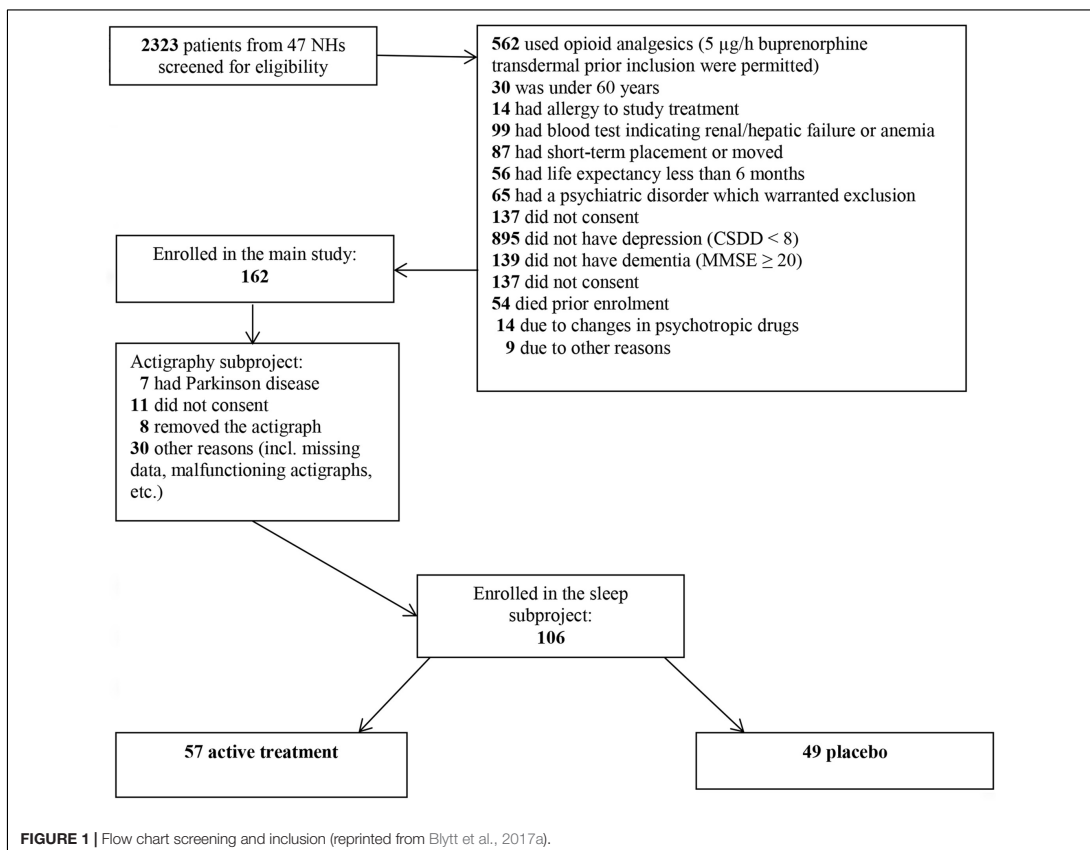


TABLE 1 | Overview of how patients were assigned to treatments.

Step	Regular analgesic treatment	Randomly assigned to either:	Dose
1	No analgesics or paracetamol ≤ 1 g/day	Paracetamol tablets	3 g/day
		Placebo tablets	Inactive placebo
2	Non-opioid analgesics/paracetamol > 1 g/day, and/or NSAID*/or no analgesics – but with difficulty swallowing tablets	Buprenorphine transdermal system	5 μ g/h (maximum 10 μ g/h)
	Buprenorphine 5 mcg/h	Placebo transdermal system	Inactive placebo system

*Except low-dose acetylsalicylic acid.

and the reason was recorded. During the study period, all patients continued their usual medical treatment.

Sleep-related outcomes were measured with *Actiwatch Spectrum (Philips Respironics)*. Activity was assessed continuously for 7 days at baseline and for 7 days in week 13 of the treatment period. The intervention started on day 8. Actigraphs were placed on the dominant/mobile wrist. As of today, there is no standard regarding the placement of the actigraph (Camargos et al., 2013). However, in prior studies in which sleep is evaluated with actigraphy, the dominant arm is most commonly used (Camargos et al., 2013). This is based on the understanding that many NH patients may have limited mobility and therefore any potential activity is more likely to occur in the dominant/mobile wrist. NH staff was instructed to push the event button on the actigraph when the patient went to bed in the evening (lights off) and got up in the morning (lights on). These instructions were given both verbally and in writing, and NH staff was provided with contact information if there were any questions regarding this procedure. The *Actiware 6 (Respironics)* was used for sleep scoring. The actigraph's sensitivity to detect motion was set to medium. Furthermore, sleep/waking status was determined for each one-minute epoch. A qualified technician scored all the activity protocols. A standardized ranked approach was applied to set rest intervals for the actigraphy data, using: event markers when possible, light and activity data, or light or activity data.

The scoring protocol generated data on the following outcome variables: total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO), early morning awakening (EMA), and number of wake bouts (NoW). These parameters were estimated in the time window between lights off in the evening and lights on in the morning. In addition, daytime total sleep time (DTS) was estimated in the time window from lights on to lights off using the *Actiware 6* software.

Pain was measured by MOBID-2 (Husebo et al., 2007), a validated, reliable staff-administered instrument with good responsiveness for measuring pain in people with advanced dementia (Husebo et al., 2007, 2014). A total score ranging from 0 to 10 was set, where 10 represented the worst possible pain. The average score was based on all of the observations during the last

week. Clinically relevant pain is defined as a score of ≥ 3 (Husebo et al., 2014).

Symptoms of depression during the last week were assessed using the validated CSDD, an instrument that consists of 19 items measuring five domains related to depression (mood, behavioral disturbances, physical signs, cyclic functions and ideational disturbances). In line with previous research, which has demonstrated that a score of 8/9 complies with the diagnosis of depression according to ICD-10 criteria, the patient had to get a CSDD score ≥ 8 to be included in the study (Barca et al., 2010). The CSDD score was provided using only information from NH staff who knew the patients well.

MMSE was used to evaluate cognitive function. MMSE is a brief, cognitive screening test with a 30-point scale that consists of 20 tasks. It was developed to distinguish potential dementia from normal functioning (Pernecky et al., 2006). Scores from 0 to 10 indicate severe dementia; from 11 to 20 indicate moderate dementia; from 21 to 25 indicate mild impairment; and from 26 to 30 indicate no dementia (Pernecky et al., 2006). A score of ≤ 20 was necessary to be included in the study.

Initially, 162 patients were included. By means of computer-generated random numbers, these patients were randomly allocated to each arm in a 1:1 ratio. A statistician produced the randomization list without any involvement from the research team. Stratification factors were not used. However, not all of the patients from the main study were included in the actigraphy subproject (see the flow chart in **Figure 1** for the reasons for inclusion/exclusion). The randomization ratio in the actigraphy subproject was therefore not 1:1. The statistician provided the research team with a blinded, sequential list of pack identification numbers, in which patients were consecutively assigned to the next pack number in the list upon inclusion. The study was double-blinded, which implied that all researchers, patients and NH staff were masked with regard to group allocation.

The patient's medical decision-making capacity was deliberated with the patient's primary nurse. For patients who had reduced capacity to give consent (MMSE scores from 16 to 19), attempts were made to modify the information. Also, the researchers contacted all of the legal guardians of eligible patients. Legal guardians who gave presumed consent on behalf of the patient received written and oral information together with a consent form to sign and mail back. The *Regional Ethics Committee (REC-West 2013/1474)* approved the study, and the study's Clinical Trial number is NCT02267057.

Statistical Analyses

Descriptive statistics (means, standard deviations and percentages) were calculated and compared across the experimental groups both at baseline (week 0) and post-treatment (week 13). In order to investigate the effect of pain treatment after 13 weeks, linear mixed models were conducted. Mixed models allow for regression-based analyses of treatment effects even in the case of considerable attrition, as long as data are missing at random (Bennett, 2001). Thus, individuals with missing data at one time point can be retained in the analyses. The mixed model for the main effect ($n = 106$) was conducted

TABLE 2 | Baseline characteristics for the different treatment groups.

	Placebo group (n = 49)	Active group (n = 57)	Total (n = 106)
Age (mean, SD)	86.0 (6.6)	85.2 (7.8)	85.5 (7.3)
Female (%)	80	74	76
MMSE (mean, SD)	6.9 (5.8)	8.2 (6.1)	7.6 (6.0)
MOBID-2 (mean, SD)	3.2 (2.3)	2.6 (1.9)	2.8 (2.1)
CSDD (mean, SD)	11.4 (4.1)	11.0 (3.4)	11.2 (3.7)

The table reports baseline characteristics for several central variables in the placebo group and the active group: age, sex, mini mental status examination score (MMSE), Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale score (MOBID-2), Cornell Scale for Depression in Dementia score (CSDD). No statistical significant differences were found between the groups.

with no covariates, with baseline as the time reference point, and with random intercept. In addition, we conducted a 2 × 2 ANOVA analysis in which we included only data from the 58 patients who completed week 13. This was done to investigate if the different analyses provided similar results.

In addition to the mixed model for the main effect, several *post hoc* sub-group analyses were carried out. Linear mixed model analyses were conducted for the sub-group of patients with MOBID-2 score ≥ 3 (n = 46) at baseline and the sub-group of patients with poor sleep at baseline, defined as sleep efficiency < 85% (Lacks and Morin, 1992) (n = 90). Finally, linear mixed model analyses were conducted to compare patients receiving active paracetamol and active buprenorphine treatment, respectively (n = 57). The statistical analyses were conducted using IBM SPSS Statistics 24.

RESULTS

Two thousand three hundred and twenty three patients were screened for potential inclusion and 106 patients were included

in the actigraphy subproject (see flow chart in Figure 1). Mean age was 85.5 years and 76% of the patients were female. Mean scores for MMSE, MOBID-2 and CSDD were 7.6, 2.8, and 11.2, respectively (see Table 2). From baseline to week 13, 48 patients dropped out of the study (reasons for dropout are listed in Table 3). There were no statistically significant differences in relevant baseline characteristics (age, sex, CSDD, MOBID-2, NPI-NH, MMSE) between the patients who dropped out (n = 48) and the patients who completed treatment through week 13 (n = 58) (see Table 4). This supports the assumption that the data were missing at random. Nine patients were using buprenorphine 5 µg/h prior to inclusion and stayed on this treatment and were then randomized to receive either an additional 5 µg/h (5 patients) or placebo patch (4 patients).

The main linear mixed model analyses for sleep outcomes showed no statistically significant differences between patients who received active pain treatment compared to those who received placebo (see Table 5). Similarly, in the 2 × 2 ANOVA

TABLE 4 | Comparison of baseline characteristics for patients who completed the treatment and patients who dropped out.

	Completed week 13 (n = 58)	Dropout (n = 48)	Total (n = 106)
Age (mean, SD)	84.5 (7.1)	86.8 (7.3)	85.5 (7.3)
Female (%)	78	75	76
MMSE (mean, SD)	7.1 (5.7)	8.3 (6.3)	7.6 (6.0)
MOBID-2 (mean, SD)	2.8 (2.0)	2.8 (2.3)	2.8 (2.1)
CSDD (mean, SD)	11.4 (3.8)	10.9 (3.7)	11.2 (3.7)

The table reports baseline characteristics for several central variables in the group of patients who completed the study period and those who dropped out; age, sex, MMSE, Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale score (MOBID-2), Cornell Scale for Depression in Dementia score (CSDD). No statistical significant differences were found between the groups.

TABLE 3 | Overview of dropout (n = 48) in week 13.

	Placebo tablets (n = 2)	Active paracetamol (n = 13)	Placebo patch (n = 11)	Active buprenorphine (n = 22)	All patients (n = 48)
Gastrointestinal	0	0	0	4	4
Neurological	0	0	0	2	2
Psychological	0	2	0	6	8
Infection	0	0	1	0	1
Falls/fractures	1	1	0	2	4
No actigraphic measure due to patient refused/malfunction	1	7	8	6	22
Patient refused to take the medication	0	3	0	0	3
Change in treatment	0	0	1	0	1
Death	0	0	1	2	3

The table reports reasons for dropout in each of the four experimental groups: active/placebo paracetamol/buprenorphine.

analyses with only the 58 patients who had complete data in week 13, there were no significant differences between active pain treatment and placebo. **Table 5** also shows descriptive statistics of sleep characteristics for both the placebo group and the active group, as measured at baseline and in week 13 of the treatment period.

Table 6 reports analyses for the subgroup of patients with pain (MOBID-2 score ≥ 3) at baseline. There were no statistically significant differences between the patients who received active treatment and those who received placebo. **Table 7** shows analyses for the subgroup of patients with sleep efficiency $< 85\%$ at baseline. Again, there were no statistically significant differences between the patients who received active treatment and those who received placebo.

Table 8 reports analyses for the subgroup of patients receiving the two different types of active pain treatment – paracetamol and buprenorphine, respectively. In this linear mixed model, there were significant effects on TST ($p < 0.01$) and SE ($p < 0.05$), which revealed that TST and SE were both improved after 13 weeks for patients who received active buprenorphine compared with patients who received active paracetamol.

DISCUSSION

This is the first placebo-controlled trial to investigate the long-term efficacy of paracetamol and buprenorphine on sleep in patients with comorbid dementia and depression. Previous studies have found that depression among NH patients with dementia may be related to untreated pain (Leong and Nuo, 2007). Moreover, it is well established that pain is associated with sleep disturbances (Chen et al., 2011; Flo et al., 2017).

Based on our findings in Blytt et al. (2017a) that pain treatment improved sleep in NH patients with comorbid dementia and depression after one week of pain treatment, we hypothesized that pain treatment would continue to improve sleep after 13 weeks in this patient group. Contrary to our hypothesis, the main mixed model analyses for the full sample showed no statistically significant differences between active and placebo treatment.

There were, however, interesting significant effects in one of the *post hoc* sub-group analyses: TST improved for patients who received active buprenorphine, compared to those who received active paracetamol. In the active paracetamol group, TST was reduced by about 10 min, while it increased by more than one hour in the active buprenorphine group. Furthermore, we found that SE was reduced in the group who received active paracetamol, while it increased by about 9% in the group who received active buprenorphine. Thus, patients who received active buprenorphine seemed to benefit from the treatment. These results are in line with Blytt et al. (2017a), wherein we also found that the group of patients who received active buprenorphine had significantly improved TST compared to the active paracetamol group after one week of treatment. However, the underlying mechanisms are unclear.

Sedation is a frequently reported opioid-associated side effect (McNicol et al., 2003). Usually, symptoms of sedation decline after a few days in more healthy adults. However, among people with comorbidity, sedation may persist (McNicol et al., 2003). In Blytt et al. (2017a), we highlight that the positive effect on TST after one week of treatment could be attributed to such a side-effect. There is a lack of studies that investigate how symptoms of sedation may persist among older people with comorbidity, and we cannot exclude sedation

TABLE 5 | Linear mixed model analyses investigating the long-term effect of pain treatment on sleep outcomes ($n = 106$).

Sleep outcomes	Treatment effect	Pre-post sleep; mean (SD)	
		Active	Placebo
TST (min)	C	515.2 (139.3) – 538.5 (142.4)	509.9 (113.6) – 498.3 (146.8)
	p	0.90	
SE (%)	C	70.0 (15.0) – 73.0 (15.3)	70.0 (13.1) – 68.5 (18.2)
	p	0.76	
SOL (min)	C	33.0 (37.3) – 31.3 (43.0)	47.0 (44.5) – 52.2 (63.5)
	p	0.61	
WASO (min)	C	134.5 (66.4) – 116.9 (51.7)	140.6 (68.3) – 133.7 (69.8)
	p	0.58	
EMA (min)	C	48.9 (60.4) – 44.4 (54.9)	30.7 (38.9) – 42.8 (45.5)
	p	0.22	
NoW (no)	C	30.3 (12.5) – 28.1 (11.5)	31.2 (11.6) – 30.7 (11.0)
	p	0.90	
DTS (min)	C	191.7 (124.0) – 206.2 (130.3)	215.8 (104.2) – 254.5 (106.5)
	p	0.15	

The table reports linear mixed model analyses for the following outcome variables: TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, wake after sleep onset; EMA, early morning awakening; NoW, number of wake bouts; DTS, daytime total sleep time. The column “Treatment effect” reports the interaction effect between treatment and time, i.e., the main result of the clinical trial, with baseline as the reference time point. C refers to coefficients and p refers to p-values. The column “Pre-post sleep; mean (SD)” reports descriptive sleep characteristics for the active and placebo groups from baseline to week 13, with standard deviations in parentheses.

TABLE 6 | Linear mixed model analyses for the subgroup of patients with pain (MOBID-2 score ≥ 3) at baseline ($n = 46$).

Sleep outcomes		Treatment effect	Pre-post sleep; mean (SD)	
			Active	Placebo
TST (min)	C	-9.71	563.5 (139.1) – 635.1 (152.2)	517.8 (122.2) – 500.8 (151.8)
	p	0.80		
SE (%)	C	-1.17	75.2 (14.4) – 80.4 (16.0)	70.5 (14.4) – 67.9 (18.4)
	p	0.77		
SOL (min)	C	7.85	23.5 (25.8) – 17.7 (32.7)	40.5 (43.6) – 49.0 (55.2)
	p	0.50		
WASO (min)	C	1.12	124.3 (71.2) – 91.7 (61.4)	138.7 (65.5) – 142.1 (73.0)
	p	0.97		
EMA (min)	C	-1.02	32.2 (35.2) – 43.5 (60.0)	36.6 (49.6) – 43.4 (51.6)
	p	0.95		
NoW (no)	C	2.03	32.2 (15.8) – 25.3 (16.0)	32.8 (15.2) – 32.5 (13.8)
	p	0.75		
DTS (min)	C	28.33	251.3 (140.3) – 253.4 (126.5)	226.8 (114.6) – 254.5 (101.6)
	p	0.39		

The table reports linear mixed model analyses for the subgroup of patients with pain (MOBID-2 score ≥ 3) for the following outcome variables: TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, wake after sleep onset; EMA, early morning awakening; NoW, number of wake bouts; DTS, daytime total sleep time. The column "Treatment effect" reports the interaction effect between treatment and time, i.e., the main result of the clinical trial, with baseline as the reference time point. C refers to coefficients and p refers to p-values. The column "Pre-post sleep; mean (SD)" reports descriptive sleep characteristics for the active and placebo groups from baseline to week 13, with standard deviations in parentheses.

TABLE 7 | Linear mixed model analysis for the subgroup of patients with poor sleep (sleep efficiency < 85%) at baseline ($n = 90$).

Sleep outcomes		Treatment effect	Pre-post sleep; mean (SD)	
			Active	Placebo
TST (min)	C	-4.81	477.1 (116.7) – 463.2 (104.9)	490.2 (95.3) – 470.4 (130.3)
	p	0.85		
SE (%)	C	-1.54	65.5 (12.5) – 65.7 (13.6)	67.7 (11.0) – 65.2 (16.9)
	p	0.64		
SOL (min)	C	-0.24	38.7 (38.7) – 45.7 (47.5)	50.1 (43.6) – 58.5 (65.0)
	p	0.99		
WASO (min)	C	3.93	153.0 (57.5) – 136.4 (40.2)	151.3 (62.5) – 147.1 (64.3)
	p	0.81		
EMA (min)	C	14.11	56.8 (63.6) – 57.7 (64.1)	33.3 (36.8) – 46.8 (46.8)
	p	0.27		
NoW (no)	C	-1.58	32.7 (11.1) – 32.0 (10.0)	32.7 (11.1) – 32.0 (12.1)
	p	0.61		
DTS (min)	C	7.74	161.6 – 167.5 (105.7 – 110.4)	205.2 (98.9) – 240.5 (110.7)
	p	0.72		

The table reports linear mixed model analyses for the subgroup of patients with sleep efficiency < 85% for the following outcome variables: TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, wake after sleep onset; EMA, early morning awakening; NoW, number of wake bouts; DTS, daytime total sleep time. The column "Treatment effect" reports the interaction effect between treatment and time, i.e., the main result of the clinical trial, with baseline as the reference time point. C refers to coefficients and p refers to p-values. The column "Pre-post sleep; mean (SD)" reports descriptive sleep characteristics for the active and placebo groups from baseline to week 13, with standard deviations in parentheses.

as a potential explanation of the results from the present study.

Importantly, we found no clear causal effect on the active group with clinically significant pain (MOBID-2 score ≥ 3), compared to placebo. This is contrary to previous studies on older people, in which sleep disturbances have been linked to untreated pain (Chen et al., 2011). In addition, pain has previously been shown to reduce SE and to increase WASO and stage 1 sleep at

the expense of slow wave sleep and REM sleep (Onen et al., 2005). It is, however, noteworthy that in the subgroup analysis including patients with clinically significant pain, all of the sleep parameters (except EMA) showed indication of improvement, compared to placebo. However, no statistically significant differences were found. This could, however, be attributed to the low number of patients with pain at baseline ($n = 46$), and we cannot exclude type 2 errors.

TABLE 8 | Linear mixed model analysis for the subgroup of patients receiving the two different types of active pain treatment – paracetamol and buprenorphine (*n* = 57).

Sleep outcomes	Treatment effect	Pre-post sleep; mean (SD)	
		Paracetamol	Buprenorphine
TST (min)	C	522.9 (149.1) – 511.4 (141.9)	
	<i>p</i>	0.01	
SE (%)	C	71.4 (14.4) – 70.2 (15.0)	68.7 (15.7) – 77.4 (15.8)
	<i>p</i>	0.03	
SOL (min)	C	–20.66	37.9 (40.0) – 41.4 (48.4)
	<i>p</i>	0.14	29.0 (35.0) – 15.6 (28.8)
WASO (min)	C	–14.91	121.6 (62.5) – 118.8 (38.4)
	<i>p</i>	0.54	145.3 (68.7) – 113.9 (70.3)
EMA (min)	C	–19.93	42.1 (46.7) – 48.2 (57.2)
	<i>p</i>	0.26	54.7 (70.1) – 38.5 (54.0)
NoW (no)	C	–10.17	28.0 (11.7) – 30.8 (8.24)
	<i>p</i>	0.07	32.2 (13.0) – 23.7 (14.7)
DTS (min)	C	44.04	173.2 (127.0) – 167.1 (124.6)
	<i>p</i>	0.10	207.2 (121.3) – 267.0 (120.9)

The table reports linear mixed model analyses for the subgroup of patients receiving active paracetamol and active buprenorphine, respectively, for the following outcome variables: TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; WASO, wake after sleep onset; EMA, early morning awakening; NoW, number of wake bouts; DTS, daytime total sleep time. The column “Treatment effect” reports the interaction effect between type of treatment and time, i.e., the main result of the clinical trial, with baseline as the reference time point. C refers to coefficients and *p* refers to *p*-values. *P*-values printed in bold denote statistical significance. The column “Pre-post sleep; mean (SD)” reports descriptive sleep characteristics for the active and placebo groups from baseline to week 13, with standard deviations in parentheses.

Limitations and Strengths

Due to the considerable attrition of patients at week 13, we conducted linear mixed model analyses. These analyses are appropriate to handle missing data and can take into account the dependency of the observations (Bennett, 2001).

There was a drop-out of 22 patients in the group who received active buprenorphine, suggesting that many patients did not tolerate such treatment (see Table 3). This large drop-out may have hindered our ability to detect a positive effect from the active treatment compared to placebo. Furthermore, it should be noted that the assignment to paracetamol or buprenorphine was not a result of randomization, but of whether the patients qualified for allocation to either paracetamol or buprenorphine at baseline (and then were randomized to either active or placebo treatment). This may produce bias by indication, since the choice of drug might be related to the outcome.

In addition, during the last decade, there has been a change in the prescription of pain medication for NH patients. Sandvik et al. (2016) found that the use of paracetamol and strong opioids increased significantly from 2000 to 2011. This affected the inclusion of patients, since patients already taking opioids could not be included in the study. Prior to inclusion, nine patients were using buprenorphine, of which five patients received active treatment and four patients received placebo treatment. This is not a source of bias since the comparison was between baseline data (pre-treatment) and week 13 (post-treatment). Therefore, any potential effects measured in week 13 will be additional effects of the treatment. However, the large drop-out in combination with the difficulty to recruit patients to the study is a threat to the generalizability of the study and we cannot exclude selection bias.

Measuring sleep with actigraphy has its limitations. Actigraphy only records movement, and a lack of movement would therefore be assessed as sleep. The study population had low SE, and previous studies show that actigraphy is less accurate in distinguishing sleep from wakefulness when SE is reduced (Sivertsen et al., 2006). Actigraphy recordings may therefore overestimate sleep relative to sleep diaries (Kushida et al., 2001; Sivertsen et al., 2006). It is therefore recommended that clinicians use sleep diaries/logs in addition to actigraphy, when evaluating sleep in NH patients. This would have strengthened the study design.

An additional limitation of the study was that we did not conduct *a priori* power analyses. The lack of this renders us unable to assess whether the statistical analyses had sufficient power. It is, however, noteworthy that our sample of patients with actigraphy was similar or larger than samples in comparable studies (Fetveit and Bjorvatn, 2005; Dowling et al., 2008; Camargos et al., 2014).

Compared to placebo, pain treatment did not improve sleep in the full sample of patients, as measured with actigraphy. However, we found a significant effect on TST and SE, when we compared the different types of active pain treatment. These results indicate that some patients may experience beneficial effects of pain treatment. However, the underlying mechanisms are unclear. The results could be an indication that some of the patients in fact experience pain, and hence had a positive effect of more potent pain treatment. Future research should investigate this further, with a larger sample size and including patients with clinically significant pain.

AUTHOR CONTRIBUTIONS

KB designed the study, analyzed the data, and wrote the paper. BB, EF, and BH designed the study, helped with the analysis of the data, and wrote the paper.

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Conflict of Interest Statement: Mundipharma International supplied the study medication, but the company did not influence the study design, data collection, analyses and interpretation of data, or final publication.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JV declared a past co-authorship with one of the authors BH.

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Appendix 9: Error notice – paper 3

In paper 3 included in this thesis, *Long-Term Pain Treatment Did Not Improve Sleep in Nursing Home Patients with Comorbid Dementia and Depression: A 13-Week Randomized Placebo-Controlled Trial* (Frontiers of Psychology, 2018), there is a minor error in the Introduction section.

On p. 2, in the final paragraph prior to the heading “Materials and Methods”, the final sentence reads:

“In the last analysis, we aimed to examine if there were any differences within the active treatment group, i.e., between patients receiving active buprenorphine and active placebo, respectively.”

Here, the word “placebo” was supposed to be “paracetamol”, as this refers to the comparison between active buprenorphine and active paracetamol. Thus, the sentence should read:

“In the last analysis, we aimed to examine if there were any differences within the active treatment group, i.e., between patients receiving active buprenorphine and active paracetamol, respectively.”

I have contacted the journal to ask them to change this in the published version of the paper.



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