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Pain and Bright Light Therapy in Nursing Home patients with Dementia

Main thesis

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Abstract

Pain, sleep disturbances and behavioural and psychological symptoms of dementia (BPSD) are common in nursing home (NH) patients with dementia. These symptoms are associated with and may trigger or exacerbate each other. NH patients with dementia have high risks of experiencing drug related adverse events. Looking for non-pharmacological treatment options is therefore vital. Light entrains the circadian rhythms and affects sleep and psychological and physiological variables in all humans including people with dementia. Bright light therapy (BLT) represents a non-pharmacological alternative for sleep disturbances and some BPSD and may also have an indirect effect on pain. The aim of this thesis was to investigate pain in a sample of NH patients with dementia. It investigated the effect of BLT on pain, and association between pain, sleep and BPSD. A linear mixed model analysis was conducted to investigate the effect of BLT over 24 weeks on pain. Bivariate correlations were conducted at baseline between pain (Mobilization – Observation – Behaviour – Intensity – Dementia 2, MOBID-2), sleep disturbances (Sleep Disorders Inventory, SDI), depression (Cornell Scale of Depression in Dementia, CSDD), agitation (Cohen-Mansfield Agitation Inventory, CMAI), BPSD (Neuropsychiatric Inventory – Nursing Home Version, NPI-NH), drug usage, and demographic variables sex and age. There was no effect of BLT on pain. Depression had a predictive effect for pain in the linear mixed model and was positively correlated with pain at baseline. Pain was correlated to total drug use, psychotropic drug use and the following BPSD variables: total NPI-NH, delusions, disinhibition, and elation. The results confirm the pain-depression relationship. Surprisingly, there was no relationship between pain sleep, and agitation, but a significant relationship between pain and delusions, disinhibition, elation, which has not been consistently found in previous research. More research is needed in examining the pain-depression dyad in NH patients with dementia, with non-pharmacological interventions targeting these symptoms.

Sammendrag

Smerte, søvnproblemer og atferd og psykologiske symptomer ved demens (APSD) er vanlig blant sykehjemspasienter med demens. Symptomene er ofte komorbide og kan utløse hverandre. Sykehjemspasienter med demens har høy risiko for ugunstige bivirkninger ved medisinbruk, og alternative ikke-farmakologiske behandlinger bør utvikles og forskes på. Lys synkroniserer døgnrytmen vår, og påvirker søvn og en rekke psykologiske og fysiologiske funksjoner også hos sykehjemspasienter med demens. Lysterapi er et ikke-farmakologisk alternativ for behandling av søvn og noen APSD, og kan indirekte ha effekt på smerte. Hensikten med denne hovedoppgaven var å undersøke smerte i et utvalg av sykehjemspasienter med demens. Effekten av lysterapi på smerte ble undersøkt, og assosiasjoner mellom smerte, søvn og APSD. Gjennom en «linear mixed model» analyse ble effekten av lysterapi over 24 uker på smerte undersøkt. Korrelasjonelle analyser ble gjennomført ved baseline (startpunktet) mellom smerte (Mobilization – Observation – Behaviour – Intensity – Dementia 2, MOBID-2), søvnproblemer (Sleep Disorders Inventory, SDI), depresjon (Cornell Scale of Depression in Dementia, CSDD), agitasjon (Cohen-Mansfield Agitation Inventory, CMAI), APSD (Neuropsychiatric Inventory – Nursing Home Version, NPI-NH), medisinbruk og demografiske variabler kjønn (sex) og alder. Det var ikke signitifkant effekt av lysterapi på smerte. Depresjon hadde en prediktiv effekt for smerte i «linear mixed model» analysen og var positivt korrelert på startpunktet. Smerte var korrelert med total medisinbruk, psykotropisk medisinbruk og følgende APSD variabler: total NPI-NH, vrangforestillinger, manglende hemning og eufori. Resultatene bekrefter smerte-depresjons dyaden funnet i andre studier. Det var overraskende at det var ingen assosiasjon mellom smerte og søvn, og agitasjon, men assosiasjoner mellom vrangforestillinger, manglende hemning og eufori noe som ikke er et konsistent funn i feltet. Mer forskning trengs for å undersøke smerte-depresjonsdyaden hos sykehjemspasienter med demens, særlig med ikke-farmakologiske behandlinger rettet mot nettopp smerte og depresjon.

Contents

Introduction

My first proper part-time job was as an unregistered nurse in the nursing home (NH) in the city district where I grew up. For the first time I was experiencing the profound need for care many NH patients have, and how loss of health, frailty and dementia could impact one's life in such a marked way. While working in a somatic long-term care unit I witnessed that the NH patients had diverse medical conditions and, although I worked in a regular long-term care unit, many had dementia.

Dementia is considered by the WHO as a public health priority due to the toll it takes on the person with the disease and the care giver as well as the substantial societal costs (Prince, 2015). Adding that the world's population is aging, and age is the strongest predictor of getting dementia, the need for evidence-based adequate care is high.

NH patients with dementia are multimorbid and frail, often with psychological and physiological symptoms further increasing disease burden. Pain, sleep and behavioural and psychological symptoms of dementia (BPSD) represent some of these symptoms, which are often treated with medications. Further, NH patients has a particularly high risk of developing drug-drug interactions and unfortunate side-effects (Fog, Kvalvaag, Engedal, & Straand, 2017; Onder et al., 2012). The development of effective non-pharmacological interventions for this group is therefore warranted.

This thesis will investigate pain, sleep and BPSD in NH patients with dementia. Furthermore, it will investigate the effects of bright light therapy (BLT) as a possible alternative to pharmacological treatments.

Background

The Nursing Home and Nursing Home Patients

This section describes the nursing home setting and clinical challenges that are commonly seen in nursing home (NH) patients. Some of the most frequent disorders in NHs; dementia, pain and sleep disturbances are described in separate sections as these are central in this thesis and therefore warrant their own thorough presentations.

The nursing home. NHs are often described as the largest institution in Norway, with care facilities for a total of 39 572 patients, including long-term units and short-term units (Nygaard, 2002; Statistics Norway, 2019). The level of care in the NH varies between countries, although some common characteristics have been found (Sanford et al., 2015). In general, countries distinguish between short-term care units and long-term care units. Short-term care or subacute care provides care service around the clock for a limited time period, often after hospital stays and often includes specialized rehabilitation services (Sanford et al., 2015). Long-term care units provide a continued service day and night aiming to provide a safe and supporting home for the patient. Long-term care is primarily for those that need assistance in activities of daily living, instrumental activities of daily living and experience disruptive behaviour as consequence of dementia (Sanford et al., 2015). Summarized, short-term care and long-term care has quite different goals, where short-term aims at rehabilitation and improving functionality, and long-term care aims at upholding functionality as long as possible as well as providing a home for the patient (Sanford et al., 2015).

In Norway, there are different types of long-term care units, and patients with moderate to severe dementia often live in specialized long-term dementia care units. These units consist of 4-12 patients per unit, where the smallest groups are for those with the most extensive needs and with poorest health (Høyland, Kirkevold, Woods, & Haugan, 2016). On average one such specialized dementia unit has 7.9 patients living there (Forskrift for

sykehjem m.v., 1988; Høyland et al., 2016). Regular long-term units in the NH do not have an upper limit of patients and consist of patients with and without dementia. Incidentally, studies suggest that around 80 % of all long-term care NH patients fulfils clinical criteria for dementia (Bergh, Holmen, Saltvedt, Tambs, & Selbæk, 2012; Røen, Selbæk, Kirkevold, Engedal, Testad, & Bergh, 2017)

Working in the NH can be challenging for the staff. The NH aims to provide a home for the patient and thus staff are heavily involved in the patients' personal lives, at the same time the patients are frail, multimorbid and have reduced communicative abilities resulting in complex medical challenges (Gautun & Bratt, 2014). In Norwegian NHs the medical personnel and competence varies, and on average there is one registered nurse per 10 patients, one licenced practical nurse per seven patients and one unskilled nurse per 16 patients during a normal day shift (Gautun & Bratt, 2014). A recent report shows an increase in general medical personnel from 2011-2016 for full-time equivalence registered physicians, registered nurses and physiotherapists with respectively increases of 31%, 17% and 22% (Melby, Ågotnes, Ambugo, & Førland, 2019). In Norwegian NHs, 24 % of the physicians are full time employed and the average NH physician is typically engaged in 49 % positions (Melby et al., 2019). On average physicians use half an hour (0.56 hour) per patient weekly in Norwegian NHs (Statistics Norway, 2019).

The nursing home patient. NH patients represent a vulnerable population with high need of treatment and care (Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Fortin, Lapointe, Hudon, Vanasse, Ntetu, & Maltais, 2004; Gautun & Bratt, 2014; Melby et al., 2019). NH patients are often multimorbid and frail (Fortin et al., 2005). Multimorbidity is commonly defined as having two or more medical conditions (Fortin et al., 2005) and is frequent in NH patients in Norway where approximately 50% have two to five diagnoses and approximately 30% have more than six (Statistics Norway, 2018). Multimorbidity is

associated with several negative outcomes including a decline in future functionality (Ryan, Wallace, O'Hara, & Smith, 2015), quality of life (Fortin, Bravo, Hudon, Lapointe, Dubois, & Almirall, 2006; Fortin et al., 2004; Makovski, Schmitz, Zeegers, Stranges, & van den Akker, 2019), and increased risk of death (Nunes, Flores, Mielke, Thume, & Facchini, 2016). In institutions in Norway, 85% of persons receiving long-term care has an extensive need for assistance (Statistics Norway, 2019). Indeed, the need for medical care services are steadily increasing for NH patients as Norwegian health reforms (Stortingsmelding nr. 47, 2008-09) has reorganised health services from secondary to primary care resulting in patients having complex medical conditions when admitted to NHs (Melby et al., 2019; Røen et al., 2017).

Pharmacological treatment and polypharmacy. Polypharmacy can be defined as taking more than five or more medications daily (Masnoon, Shakib, Kalisch-Ellett, & Caughey, 2017) and prevalence in the general elderly population in Norway is high, with 67% over the age of 65 using more than five medications (Folkehelseinstituttet, 2014b). Studies have found that Norwegian NH patients on average receive up to nine drugs on a regular basis (Fog et al., 2017; Gulla, Flo, Kjome, & Husebo, 2018), and there is a high psychotropic drug usage (Gulla, Selbaek, Flo, Kjome, Kirkevold, & Husebo, 2016; Halvorsen, Selbæk, & Ruths, 2017; Helvik, Šaltytė Benth, Wu, Engedal, & Selbæk, 2017). A study examining polypharmacy in 57 NHs across 8 countries observed polypharmacy in 49.7% of the NH patients and excessive polypharmacy (>9 drugs per day) in 24.3% of the NH patients (Onder et al., 2012). In addition, the study found that excessive polypharmacy was associated with chronic diseases and symptoms of depression, pain, dyspnoea and gastrointestinal symptoms

as compared to non-polypharmacy (Onder et al., 2012). Polypharmacy in NH patients with severe cognitive impairment is associated with increased mortality (Onder et al., 2012).

Dementia

Dementia is a terminal disorder characterized by decline in cognitive function, causing impairment in a person's functioning (activities of daily living) (American Psychiatric Association, 2013; World Health Organization, 2017). The decline in function and cognitive performance is beyond that of normal ageing (McKhann et al., 2011). In the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) dementia is classified as "Neurocognitive Disorders" with a number of etiological subtypes. A common feature of these disorders is that the primary clinical deficit is in cognition, which is acquired not developmental, and distinct from other mental illness. Common neurocognitive domains affected are i) complex attention, ii) executive function, iii) learning and memory, iv) language, v) perceptual-motor abilities, and vi) social cognition. (American Psychiatric Association, 2013). The International Classification of Diseases (ICD-10) has similar, but not identical criteria (World Health Organization, 1992).

Types of dementia. Dementia denotes multiple different conditions that are classified based on the underlying pathology for each subtype (American Psychiatric Association, 2013). Importantly, as symptoms overlap significantly between the different types, diagnosing can be difficult. Brain imaging and biomarkers are more detailed, but this is usually not readily available for practitioners. Indeed, mixed dementia has been found to be the most common type of dementia in NH patients (Scherder et al., 2003), and research comparing post-mortem examination and diagnosis suggest that mixed dementia is more common than "pure" dementia subtypes (Bowler, Munoz, Merskey, & Hachinski, 1998; Jellinger, 2006; Leiros et al., 2018). Nevertheless, the two most common types of dementia are considered to

be Alzheimer's disease (AD) and Vascular dementia (VaD), although prevalence varies between studies and nations (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012).

Alzheimer's disease is a neurodegenerative disorder caused by accumulation of amyloid B and tau protein that mediate neuronal dysfunction (Petit, Montplaisir, Louis, & Boeve, 2017). The neurodegeneration develops gradually and affects memory functions early in the development of the disorder. Memory, mood and eventually sleep functions are affected as the neurodegeneration becomes widespread in the brain (Petit et al., 2017). Interestingly, sleep could have a protective role in warding off toxic protein accumulation, as studies have demonstrated that the brain's glymphatic system has higher clearance of amyloid B during sleep and anaesthesia compared to wakefulness (Xie et al., 2013).

Vascular Dementia is caused by haemorrhagic or ischemic strokes in the blood vessels of the brain, hindering blood flow to the brain (Prince, 2015). This type of dementia typically develops more abrupt and intermittently than AD, depending on the brain area that is affected, the severity and type of disruption. A major risk factor in VaD is general high blood pressure, and cardiovascular diseases (Khan, Kalaria, Corbett, & Ballard, 2016).

Parkinson disease (PD) with dementia and dementia with Lewy bodies are dementia as a result from neurodegeneration related to α-syneucleinopathy (Petit et al., 2017). PD is a neurodegenerative disorder characterized by rigidity, resting tremor, bradykinesia and impairment in postural reflexes and gait. This is primarily caused by neurodegeneration in dopaminergic neurons in the substantia nigra (Petit et al., 2017). The incidence of dementia in PD is relatively high, with 80% of a non-demented PD population developing dementia within 8 years (Aarsland, Andersen, Larsen, & Lolk, 2003). Lewy-body dementia is characterized by progressive cognitive decline, spontaneous parkinsonism, hallucinations and variable vigilance, this is caused by the presence of Lewy bodies in the limbic and neocortical areas in the brain (Petit et al., 2017).

Frontotemporal dementia (FTD) is a neurobehavioural disorder associated with the accumulation of tau protein (similarly to AD), with the neurodegeneration specified to the frontal and temporal lobes of the brain (Petit et al., 2017). It debuts more often in younger people (before the age of 70 years) than other dementia types (Reneflot, Aarø LE, Aase H, Reichborn-Kjennerud T, Tambs K, & S., 2018). As with AD, FTD patients show sleep disturbances in the sleep-wake rhythm associated to the alpha rhythm (Merrilees, Hubbard, Mastick, Miller, & Dowling, 2009).

Prevalence and societal impact. Dementia afflicts 46.8 million people worldwide, a number estimated to be 135.5 million in 2050 (Prince, 2015). Based on population studies in other countries and numbers from the World Health Organisation (WHO) (Prince, 2015), it is estimated that between 80 000 and 104 000 people suffer from dementia in Norway today (Reneflot et al., 2018). On a global scale the specific age-related prevalence in dementia almost doubles every 5 years, with a prevalence of approximately 1.5% in persons aged 60-69 years to 40% in persons over the age of 90 (Qiu, De Ronchi, & Fratiglioni, 2007). The global societal cost of dementia were estimated at a US$818 billion in 2015, a 35% increase since 2010 (Wimo et al., 2017), making this particular disorder a public health priority due to its impact on global economy, as well as the toll it takes on patients, family and caregivers (Wimo & Prince, 2010). In Norway, over 80 % of patients living in NHs have dementia, as well as 40 % of those over 70 years receiving home care services. The latter does not include those who live with the disorder without receiving services (Folkehelseinstituttet, 2014a; Røen et al., 2017; Selbæk, Kirkevold, & Engedal, 2007). AD is the most common form of dementia with 60-80% of people with dementia having this form (Thies & Bleiler, 2013). VaD is found in approximately 20-25% of patient cases (Qiu et al., 2007). A cohort study of Norwegian NH patients found that 71 % had AD, 7.9 % VaD, 1.9 % had AD and VaD, 8.1% had frontotemporal dementia, 3.7% had dementia with Lewy bodies and 7.4% had other types

of dementia (Røen et al., 2017). The low prevalence of mixed dementia illustrates the aforementioned difficulty in diagnosing correctly the different types of dementia. A study examining people with dementia post-mortem through autopsy found that from the 660 AD suspected cases, 93% had AD pathology, however less than half of the confirmed AD cases had "pure" AD (Jellinger, 2006). Furthermore, Røen et al. (2017) found that 83.8% had dementia, but only 55.9% had an existing dementia diagnosis in their medical record. This is in accordance with previous findings (Bergh et al., 2012; Selbæk et al., 2007).

Behavioural and psychological symptoms of dementia (BPSD). BPSD or neuropsychiatric symptoms (NPS) are common in people with dementia, affecting up to 90% of patients during the course of their disease (Bergh et al., 2012; Selbæk et al., 2007). BPSD may be defined as: "symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia" (Finkel & Burns, 1999, as cited in International Psychogeriatric Association, 2012, Module 1, p. 5). BPSD include behaviours such as aggression, sleeplessness and agitation, and psychological symptoms such as depression, anxiety and euphoria, psychosis symptoms and apathy (American Psychiatric Association, 2013; Finkel, 2000; Finkel, Costa E Silva, Cohen, Miller, & Sartorius, 1996). BPSD greatly impact the patient, family and caregivers, and are associated with early institutionalising, more use of coercion and increased psychopharmacological interventions in people with dementia (Finkel, 2000; Finkel et al., 1996; Kirkevold, Laake, & Engedal, 2003; Sourial, McCusker, Cole, & Abrahamowicz, 2001). BPSD are found in every type of dementia, each dementia type with its own characteristic symptoms (Finkel, 2000). For instance, in the early stages of Alzheimer's and vascular dementia, depression and anxiety are common, whereas euphoria often is present in frontotemporal dementia (American Psychiatric Association, 2013; Chiu, M.-J., Chen, Yip, Hua, & Tang, 2006). Bergh et al. (2012); Selbæk et al. (2007) found that the severity of neuropsychiatric symptoms increases

with higher severity of dementia. Additionally, in the NH population in Norway, NH patients with dementia were reported to experience more severe and more neuropsychiatric symptoms than NH patients without dementia (Bergh et al., 2012; Røen et al., 2017).

Depression is characterized by prevalent depressed mood and loss of interest in things that the individual used to have interest in (American Psychiatric Association, 2013). In people with dementia it is frequent, with approximately 40-60% expressing depressive symptoms (Garre-Olmo et al., 2003). Depression symptoms in people with dementia is associated with distress, reduction in quality of life, increase in cognitive and functional impairment, increased mortality and carer distress and carer depression (González-Salvador et al., 2000; Livingston et al., 2017).

Sleep disturbances are one of the more troublesome BPSD symptoms and about 25-55% of people with dementia have been found to experience sleep problems (Dauvilliers, 2007; Moran, Lynch, Walsh, Coen, Coakley, & Lawlor, 2005). The disrupted and fragmented sleep pattern, especially during nighttime sleep increases caregiver distress (Neikrug & Ancoli-Israel, 2010; Wulff, Gatti, Wettstein, & Foster, 2010). The underlying causes are varied, such as pain (Flo, Bjorvatn, Corbett, Pallesen, & Husebo, 2017), mood disorders (Ownby, Peruyera, Acevedo, Loewenstein, & Sevush, 2014), lack of activity (Neikrug & Ancoli-Israel, 2010), and direct neurodegenerative changes related to specific dementia (Petit et al., 2017). Sleep disturbances predicts depressive symptoms in carer and increases carer burden (Neikrug & Ancoli-Israel, 2010).

BPSD show a circadian pattern and this is referred to as “sundowning” (Gnanasekaran, 2016). This is a term describing the worsening of BPSD in the late afternoon and evening, including agitation, confusion and nightly wanderings. This is associated with a disrupted circadian rhythm in patients with dementia, which again is associated with cell atrophy and decreased function in brain areas responsible for circadian rhythm

(Gnanasekaran, 2016; Song, Dowling, Wallhagen, Lee, & Strawbridge, 2010). Sundowning causes a lot of distress for both caregiver and the patient, and increases the probability of institutionalising (Neikrug & Ancoli-Israel, 2010).

Factors causing BPSD. In addition to the direct influence of dementia neuropathology causing BPSD, several biopsychosocial factors also influence development and expression of BPSD. Three theoretical viewpoints are commonly used to understand BPSD (International Psychogeriatric Association, 2012), these are; learning theory (Spence, 1956), the unmet needs model (Cohen-Mansfield, 2000; Cohen-Mansfield, Dakheel-Ali, Marx, Thein, & Regier, 2015) and stress/environmental vulnerability (Smith, M., Gerdner, Hall, & Buckwalter, 2004). The different theoretical viewpoints do not exclude each other, and interventions can address BPSD from all three viewpoints.

The behavioural and learning theory postulates that rewarded behaviour intensifies and increases. This is based on foundational psychological learning principles, such as classic and operant conditioning (Spence, 1956). As an example, staff may unintentionally reward a disturbing behaviour by giving attention to the patient when he or she is screaming or wandering. While giving attention to patients, in this case reward, when patients are quiet may reduce the disturbing behaviour (International Psychogeriatric Association, 2012).

The unmet needs model postulates that challenging behaviours may arise from underlying unmet human needs. These include needs for meaningful activity, emotional validation and sociability. Further, the theory proposes that these needs may not be met as a result from the deteriorating ability to communicate and decreased ability to use the environment to accommodate these needs (Algase et al., 1996; Cohen-Mansfield & Deutsch, 1996; Cohen-Mansfield & Werner, 1995). See Figure 1 for a more detailed description of the theory.

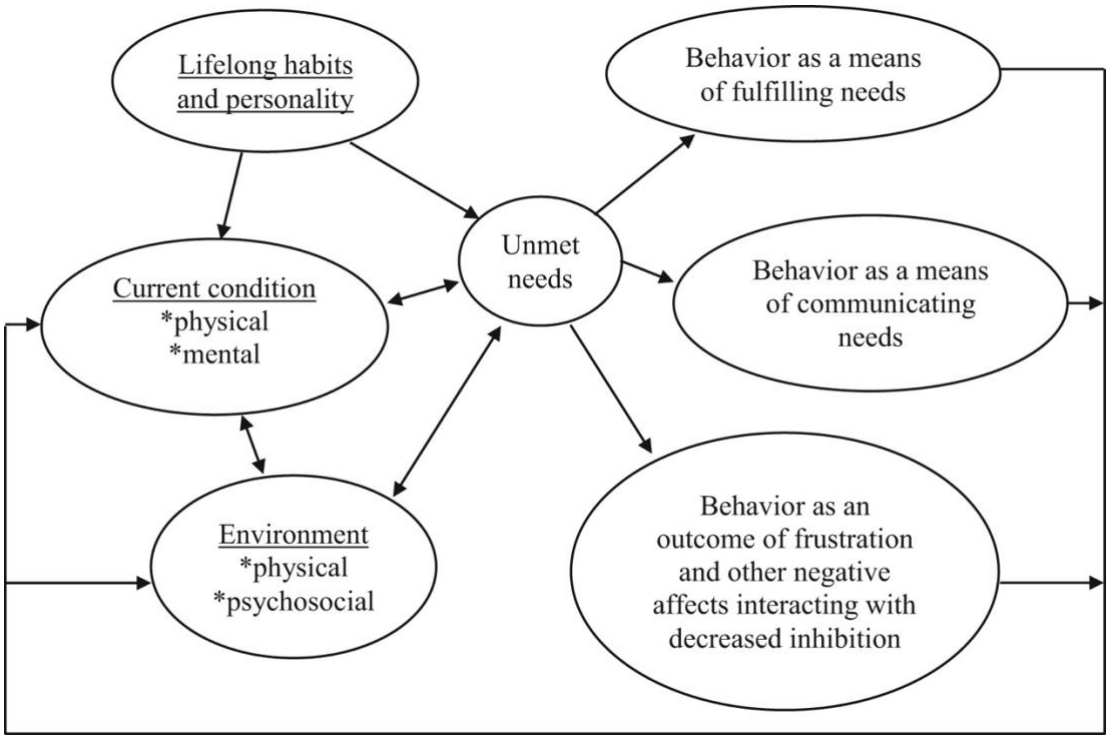


Figure 1: *Unmet needs model of problem behaviors* 1.

1: From "Which Unmet Needs Contribute to Behavior Problems in Persons with Advanced Dementia?" by J. Cohen-Mansfield, M. Dakheel-Ali, M.S. Marx, K.Thein, N.G. Regier, 2015, *Psychiatry Research*, *228*, pp. 59-64. Copyright 2015. Reprinted with permission from Elsevier.

Environmental vulnerability or lowered stress threshold model postulates that dementia reduces a person's coping abilities and the environment is experienced as increasingly more stressful during the course of the dementia disorder (Smith, M. et al., 2004). Different environmental factors exceed the threshold for stress in the person with dementia resulting in anxiety and challenging behaviours. More specifically this could result from decrease in comprehension, confusion, fatigue, change in routine and more (Cohen-Mansfield, 2001; International Psychogeriatric Association, 2012; Smith, M. et al., 2004).

Pain

Pain is a highly prevalent condition in old age and in NH patients. The International Association for the Study of Pain (IASP & International Association of the Study of Pain, 2017) defines pain as "an unpleasant sensory and emotional experience associated with actual

or potential tissue damage, or described in terms of such damage" (para. 3). Thus, pain is an individual and subjective experience. It is common to categorize pain into nociceptive and neuropathic pain. Nociceptive pain is defined as: "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" (IASP & International Association of the Study of Pain, 2017, para. 28), and includes somatic (musculoskeletal) and visceral (internal organs) pain. This is the pain typically felt if an individual has an injury or inflammation. Neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system" (para. 25). The central or peripheral nervous system is damaged, and this abnormal functioning causes pain sensation (IASP & International Association of the Study of Pain, 2017). A number of cognitive and psychosocial factors have been found to influence the experience of pain, and biopsychosocial models try to explain the interplay between biological, psychological (herein cognitive, emotional and learning behaviour) and social factors (Asmundson & Wright, 2004; Gibson & Helme, 2000). Furthermore, psychological treatments for chronic pain have shown small, but significant effects in older adults, specifically in decreasing pain experience and catastrophizing beliefs, and improving self-efficacy for management of pain (Niknejad et al., 2018).

Pain and depression are often comorbid and may exacerbate each other. Indeed, people with chronic pain have higher risk for developing depression, and vice versa, people with depression are at risk of painful somatic complaints (Bair, Robinson, Katon, & Kroenke, 2003; Goldenberg, 2010). This relationship is referred to as the pain-depression dyad, and pain and depression are found to share neuronal pathways, neurotransmitters and respond to similar treatments (Chopra & Arora, 2014; Woo & Wager, 2015).

Pain in people with dementia. Pain in people with dementia is common and approximately 40-60% of NH patients experience persistent pain (Achterberg et al., 2010; Husebo, Strand, Moe-Nilssen, Husebo, Aarsland, & Ljunggren, 2008). Pain in people with

dementia is a complex phenomenon due to the varying types of dementia, pain sensations, and the underlying neuronal mechanisms in both conditions (Scherder, Herr, Pickering, Gibson, Benedetti, & Lautenbacher, 2009).

Several clinical studies have shown that NH patients with dementia are more prone to receive undertreatment of pain than NH patients without dementia (Achterberg et al., 2010; Husebo et al., 2008; Morrison & Siu, 2000; Scherder & Bouma, 1997; Scherder et al., 2009). However, recent studies report a change in prescribing of analgesics in NH patients with dementia, with increasing usage trends, showing similar analgesics usage in NH patients with and without dementia (Sandvik, Selbaek, Kirkevold, Husebo, & Aarsland, 2016; Tan et al., 2016). This is not without concern, as there is high prevalence of polypharmacy in NH patients with dementia (Onder et al., 2012), as well as the potential side and adverse effects of medications in these patients (Tune, 2001). It is also uncertain whether the increased use of analgesics in people with dementia represents a targeted pain treatment, or a general increase of prescribing analgesics. In other words, it is not certain that the right patient receives the right dose of analgesic treatment (Husebo, Achterberg, & Flo, 2016). It is therefore important to consider potential adverse events and review pharmacological treatment regularly in these patients.

Neuropathology may impact pain processing in people with dementia in various ways. In AD it seems that the sensory cortex is intact until severe stages of the disease (Defrin et al., 2015), and studies have proposed that in early to moderate stages of AD, VaD and mixed dementia, patients experience pain stimuli similar to controls (Scherder et al., 2009). However anticipation of pain and communication of pain seems to be impaired due to cognitive decline (Benedetti, Arduino, Vighetti, Asteggiano, Tarenzi, & Rainero, 2004). Regions affected in neurodegeneration in dementia are also involved in pain processing, and in PD with dementia neuronal damage is associated with increased pain sensitivity. In addition, damage to limbic

structures could decrease motivational factors to retract from painful stimuli (Defrin et al., 2015). A review on pain processing in cognitive impairment, including neurodegenerative diseases concludes that people with cognitive impairment experience pain stimuli, and furthermore that there is more evidence for hypersensitivity than hyposensitivity. Summarizing, there seems to be no indication that people with dementia should experience less pain than people without dementia (Defrin et al., 2015).

As mentioned, cognitive and psychosocial factors mediate the pain experience and as people with dementia gradually loses their cognitive abilities this could potentially affect how they cope with pain. Anticipation of painful events and memory functions are severely impaired in advanced stages of dementia, and this could enhance confusion, the frequency of painful events and the emotional distress experienced. For instance, a person with severe dementia could forget that he or she has an injury, such as a fraction. Therefore, he or she would potentially engage in behaviour, like putting pressure on a fraction while getting up, which would cause increased pain and hinder rehabilitation. Such situations would not only be painful, but also confusing and frightening for the person. Additionally, people with dementia has reduced ability to engage in cognitive coping mechanism for pain, such as self-efficacy and trust in help personnel (Gibson & Chambers, 2004).

Pain assessment in people with dementia. Pain is subjective and self-report is considered to be the "gold standard" of pain assessment (Bendinger & Plunkett, 2016; IASP & International Association of the Study of Pain, 2017). Pain is complex and multidimensional and the large number of pain assessment scales available reflects this. As any assessment scale measuring tool these should have sufficient validity, sensitivity, specificity and reliability (Bendinger & Plunkett, 2016). Furthermore, the complex and multidimensional nature of pain makes a number of aspects relevant in pain assessment.

These include acute and chronic pain, mood and affect, pain coping, quality of life, functionality and pain communication ability (Bendinger & Plunkett, 2016).

One of the most common pain assessment scales is Visual Analogue Scale (VAS), a subjective self-report scale (Price, McGrath, Rafii, & Buckingham, 1983). The individual scores the symptom, in this case pain, by putting a mark along a line with total score between 0-100 (in millimetre). VAS reliably measures change in pain, but is not reliable in measuring pain between patients, as people with the same degree of sickness measures differently with the VAS, a 4 is not a 4 (Tyrdal & Ræder, 2015). This makes research with this scale problematic, as it is not a quantifiable measurement. VAS demands that the individual understands the task (Tyrdal & Ræder, 2015), a potential challenge when conducting assessment with individuals with communicative challenges.

Pain assessment is considered a major clinical challenge in people with dementia (Corbett et al., 2012). When defining pain, the IASP and International Association of the Study of Pain (2017) states in additional text that the ability to verbally communicate pain is not necessary for experiencing pain and having the need for pain-relief. This additional note addresses a core challenge in reliable assessment in people with dementia, and as self-report is the gold standard of pain assessment, non-verbally or less communicative persons may not report, remember and understand the experienced pain accurately. This is further reflected in The guidelines of the American Geriatrics Society, AGS Panel on Persistent Pain in Older Persons (2002) that recommends self-report assessment when this is possible to provide. However, in moderate to severe dementia, or in non-verbal patients, the guidelines states that "the practitioner should attempt to assess pain via direct observation or history from caregivers.", and recommend observations and evaluation of facial expressions, verbalisation and vocalisations, body movements, interpersonal interactions, changes in activity or routine and mental change. Observational pain assessment scales are therefore necessary for pain

assessment in people with dementia, and others that are not able to self-report accurately (Husebo et al., 2016). This may be done by a proxy rater, usually health personnel or caregiver that knows the patient well, that can accurately interpret the patient's behaviour and fill out a structured pain assessment tool, and thus provide reliable and valid data (Husebo, Strand, Moe-Nilssen, Snow, & Ljunggren, 2007).

Circadian Rhythms and Sleep

From a behavioural perspective, sleep is a behavioural state characterized by perceptual detachment and unresponsiveness to the environment (Carskadon & Rechtschaffen, 2017). Normal human sleep is divided into two physiological states, rapid eye movement (REM) sleep and non-REM (NREM) sleep, alternating during the sleep period, in a cycle of 90-110 minutes. These are defined by objective sleep measurements from polysomnography (PSG) data and usually consists of several physiological measurements; electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). In addition, it is common to measure pulse through electrocardiogram (ECG) and several respiratory measures (Carskadon & Rechtschaffen, 2017). See Textbox 1 for a detailed description of the stages in NREM and REM.

Textbox 1: *Description of the different sleep stages.*

NREM[1]:

- N1[1]: Lasts a few minutes. The transition from wakefulness to sleep. EEG[1]: rhythmic alpha-waves changes to low-voltage, mixed frequency pattern
- N2[1]: Follows N1. EEG: K complexes and sleep spindles
- N3[1]: Slow wave sleep (SWS), former stage 3 and 4. EEG: high voltage slow waves, delta-waves.
- Body: inactive throughout NREM.

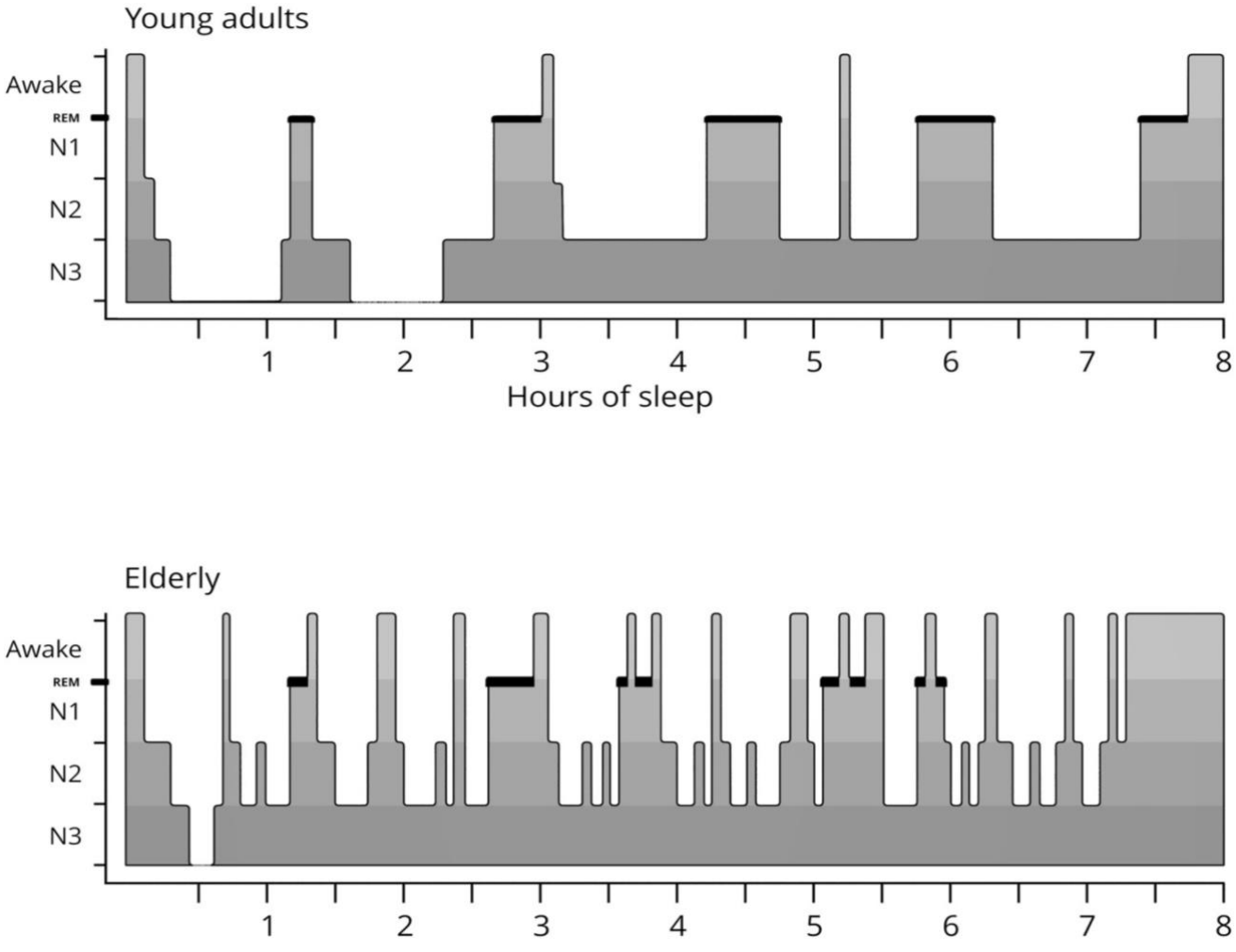
REM[1]:

- EEG[1]: active, similar to wakefulness
- EOG[1]: active eye movement
- Body: high pulse and muscle atonia
- Most dreaming occurs

1: Abbreviations in introduced order: NREM: non-Rapid eye movement sleep, N1, N2 and N3 refers to NREM stages 1, 2 and 3 respectively. EEG: Electro Encephalogram, REM: Rapid eye movement, EOG: Electro Oculogram.

Sleep architecture is the term commonly used for the cyclic pattern of going in and out of the different sleep stages during the biological night. A sleep hypnogram shows the sleep architecture throughout the biological night. Figure 1 depicts a normal night's sleep in a young adult. In the elderly adult there are several changes in sleep architecture that are common, this is also shown in Figure 1. As shown in the Figure 1 hypnogram of sleep in old age, deep sleep is less pronounced and is replaced by more time in the lighter sleep stages, which can cause more nightly awakenings (Bliwise & Scullin, 2017). Most age dependent changes happen before 60 years, however challenges connected with other medical conditions, pain or pharmacology can enhance these changes (Bliwise & Scullin, 2017; Flo et al., 2017).

Figure 1. *Hypnogram of night sleep cycle in young adults and elderly adults*



Regulation of sleep and circadian rhythms. Sleep-wake regulation is an interaction of a circadian process, a homeostatic process and behavioural factors (Borbély, 1982; Borbély & Achermann, 1999). The circadian process interacts with the homeostatic process to influence a variety of physiological variables, including the timing and internal structure of sleep (Czeisler & Buxton, 2017). Environmental, genetic, social, neuronal, age-related, pharmacological and behavioural factors all influence this system of sleep regulation.

The homeostatic factor is the build-up of sleep pressure as a result of prior time spent awake. Insufficient amount of sleep results in a stronger homeostatic pressure, experienced need, for sleep in the individual (Bjorvatn & Pallesen, 2009).

Circadian clocks (or circadian oscillators) are characterized by an endogenous rhythm, averaged to slightly more than 24 hours, that persists independently of small changes in environment and behaviour (Czeisler & Buxton, 2017). The main circadian clock in humans is the suprachiasmatic nuclei (SCN), also called the master clock. Located in the anterior hypothalamus, the SCN drives prominent circadian rhythms in an array of physiological variables, such as core temperature and hormone secretion and activation. For instance, melatonin levels increase during evening time and reaches highest during the night, and then decreases approaching waking time, and symbolizes the body response to darkness (Czeisler & Buxton, 2017).

Light and the circadian rhythm. The SCN is influenced by external stimuli, called zeitgebers, that provide input for syncing the circadian rhythm to 24 hours sleep-wake schedule (Czeisler & Buxton, 2017). Light is the main environmental stimuli and has been found to influence the circadian system, wakefulness, mood and cognition (LeGates, Fernandez, & Hattar, 2014). Non-visual photoreception starts with the intrinsically photosensitive retinal ganglion cells (ipRGCs) in the retina, they convey information about the light into neural activity, relayed through a retinohypothalamic tract through these same

photosensitive cells to the SCN (Berson, Dunn, & Takao, 2002; Tosini, Ferguson, & Tsubota, 2016). An output pathway from the SCN, passes through the spinal cord, to the pineal gland provides input to the pineal gland which further influences the secretion of hormones, such as melatonin (Czeisler & Buxton, 2017; Zeitzer, Dijk, Kronauer, Brown, & Czeisler, 2000). The influence light has on a number of physiological variables may be called non-image forming (NIF) visual functions or non-visual effects (LeGates et al., 2014).

Qualities of the light that have been found to influence the degree of these non-visual effects are coloration, timing, intensity, duration and history of light exposure. Blue and short-wavelength green light has the strongest effect on melatonin suppression and syncing abilities (Czeisler & Buxton, 2017; Takahashi, DeCoursey, Bauman, & Menaker, 1984), further it has direct effects on mood and learning (Fernandez et al., 2018; Tosini et al., 2016)

Light exposure during the biological nighttime has the strongest impact on non-visual effects. On average 2.3 hours before waking time the core body temperature cycle reaches its lowest, this point is called nadir (Czeisler & Buxton, 2017). If an individual is exposed to light before nadir, the evening and early night, this tends to advance the circadian phase, and if light exposure occurs after nadir, early morning, this delays the circadian phase. This is called a phase-response curve (Khalsa, Jewett, Cajochen, & Czeisler, 2003).

Light intensity and light exposure duration influence the degree of non-visual effects. Stronger intensity results in larger effects where a study has shown a non-linear relationship where at 50 lux there was a resetting response of the circadian rhythm, with maximal slope (increase in effect) at 100 lux and maximal changes at 500 lux (Zeitzer et al., 2000). Furthermore, light pulses on three consecutive days resulted in a larger changes than one light pulse (Czeisler & Buxton, 2017; Zeitzer et al., 2000). Light pulse duration followed a non-linear dose-dependent curve where shorter bright light exposure resulted in higher degree of delays in circadian rhythm, higher acute melatonin suppression and inducing alertness than

longer light exposures to the retina (Chang et al., 2012). Lastly, photic history, the exposure to light prior to a light exposure influences non-visual effects, where dim light (1 lux) seems to sensitise the circadian clock to the effect of a light pulse as compared to typical room light (90 lux) (Chang, Scheer, & Czeisler, 2011).

Neurodegenerative disease, circadian disruption and sleep problems. Circadian rhythms and sleep in neurodegenerative diseases are associated to abnormal patterns in timing and internal structure of sleep. As neurodegenerative diseases affect brain regions and neurotransmitters involved in sleep-wake regulation, sleep disruption becomes the result. Treatment of disturbances in timing and internal structure of sleep could be a possible approach for improving symptoms in dementia and neurodegenerative disorders. It may even slow the debilitating progression of the disease (Figueiro et al., 2014; Skjerve, Bjorvatn, & Holsten, 2004; Skjerve, Holsten, Aarsland, Bjorvatn, Nygaard, & Johansen, 2004).

In patients with AD 25 % of patients with mild to moderate AD experience sleep disturbances and about 50% in patients with moderate to severe AD. Several types of sleep problems, with multifactorial causes are common: insomnia, excessive daytime sleepiness, difficulties falling asleep and maintaining sleep – caused by frequent awakenings during night time and early awakening in mornings (Peter-Derex, Yammine, Bastuji, & Croisile, 2015). The neuropathology of AD affects many brain areas of sleep and circadian control, including the anterior hypothalamus (SCN and ventrolateral preoptic area), and AD patients show a higher neuropathology in the SCN than age corresponding patients without AD (Hofman & Swaab, 1994). A study by Xie et al. (2013) found that the dissolution of tau protein is higher during sleep than when awake, and thus good sleep could potentially be a proactive factor for AD disease.

Patients with VaD show similar prevalence of sleep disturbances as AD patients, however patients with cortical VaD had a slightly higher prevalence of sleep disturbances and

BPSD (Fuh, Wang, & Cummings, 2005). Obstructive sleep apnoea (OSA) is associated with VaD and cardiovascular diseases, and could be a risk factor for recurrent strokes (Ramos, Dib, & Wright, 2013). Treating sleep disorders in the elderly population could prevent further cardiovascular diseases and consequently reduce the risk of VaD (Ramos et al., 2013).

In PD with dementia and Dementia with Lewy-bodies sleep disturbances are one of the most common non-motor symptoms, and as the disorder advances so do sleep disturbances. The most common sleep problem is REM-sleep behaviour disorder (Comella, 2007). REM-sleep behaviour disorder is characterized with the affected individual acting out dreams during REM-sleep, REM-sleep occurring without muscle atonia (Peter-Derex et al., 2015). REM-sleep behaviour disorder could be an early manifestation of neurodegenerative disorders including PD with dementia and dementia with Lewy-bodies. In some long-term follow-up studies, 6-15 years, the risk of developing neurodegenerative disorders in REM-sleep behaviour disorder patients is 41-91.9%, noting that development can be highly different from person to person (St Louis, Boeve, & Boeve, 2017).

Circadian rhythms in patients with dementia and NH patients. The circadian rhythm regulation seems to be disrupted in people with dementia, and research has found changes in sleep-wake pattern, core-temperature and melatonin rhythm (Peter-Derex et al., 2015). As mentioned above there are several neuropathologic underpinnings that influence sleep-wake disturbances in patients with dementia. However, circadian rhythms are also regulated by environmental factors, such as light and exercise. NH patients are shown to have less activity during the day and are less exposed to daylight (Neikrug & Ancoli-Israel, 2010). The reduced sensory input is likely to lower the general level of activation which is considered an important factor in the circadian rhythm control. An environment weak in external stimuli together with a poor sensory sensitivity due to neurodegeneration, may make the NH patient more vulnerable to developing circadian dysregulation (Burns, Allen, Tomenson, Duignan, &

Byrne, 2009). This can in turn affect the risk of cognitive dysfunction, behavioural disturbances, functional impairment and depression in people with dementia (Neikrug & Ancoli-Israel, 2010).

Sleep assessment. Sleep assessment can be challenging in NH patients with dementia. Indeed, a number of objective and subjective assessment tools will not provide valid and reliable assessments in this population (Blytt et al. 2017). Polysomnography is considered the "gold standard" of objective sleep assessment as it is highly detailed and can be adapted to include a wide variety of physiological measurements. Polysomnography often has to be conducted in a laboratory and elderly participants, including NH patients with dementia does often not tolerate this elaborate method (Stone & Ancoli-Israel, 2017). Actigraphy assess the sleep-wake cycle based on inactivity-activity movements and is usually measured with a watch-like device worn on the wrist (sometimes leg). Actigraphy provides 24-hours measurement over days, weeks or months, and is less expensive than PSG. Actigraphy is commonly tolerated in NH patients (Stone & Ancoli-Israel, 2017). Studies indicate that actigraphy may overestimate sleep when sleep efficiency is impaired, particularly if the participants lie still for longer periods of time (Kushida, Chang, Gadkary, Guilleminault, Carrillo, & Dement, 2001). This may be the case with NH patients with decreased mobility and high prevalence of pain. Self-report continues to be an important sleep measurement tool in the cognitively healthy population (Carney et al., 2012), but as previously mentioned self-report has validity issues when used in people with dementia. Proxy-rater assessment tools validated for this population is useful to assess sleep. As with pain, it is important that the proxy-rater is familiar with the person being assessed in order to detect changes in behaviour. Proxy-rater assessment scales commonly used in NH compared to actigraphy measurements seems to underreport sleep disturbances (Blytt, Bjorvatn, Husebo, & Flo, 2017), however more specific sleep assessment scales, such as Sleep Disorders Inventory (SDI) has been

shown to have good correlation with actigraphy and PSG data in examining sleep disturbances in people with dementia (Tractenberg, Singer, Cummings, & Thal, 2003).

The Relationship Between Pain, Sleep and Mood Disorders (BPSD)

A large body of evidence suggests that pain and sleep are related in a reciprocal relationship (Doufas, 2017). Research from animal studies (Finan, Goodin, & Smith, 2013), experimental studies in healthy subjects (Haack, Lee, Cohen, & Mullington, 2009) and in longitudinal, epidemiological and treatment studies in clinical populations (Doufas, 2017; Smith, M.T. & Haythornthwaite, 2004; Tang, McBeth, Jordan, Blagojevic-Bucknall, Croft, & Wilkie, 2013; Ødegård, Sand, Engstrøm, Zwart, & Hagen, 2013) support the notion of a bidirectional relationship, where pain and sleep problems exacerbate each other.

Furthermore, mood disorders, specifically depression and anxiety, seem to be a comorbid link between pain and sleep disturbances. People with mood disorders commonly experience abnormal sleep patterns (Ford & Kamerow, 1989) and people with chronic pain often experience mood disorders (Taylor, Mallory, Lichstein, Durrence, Riedel, & Bush, 2007). The interaction of pain, abnormal sleep and mood dysfunction is complex and has been suggested in a number of studies in different contexts (Castillo et al., 2013; Jansson-Fröjmark & Boersma, 2012; Lallukka, Øverland, Haaramo, Saastamoinen, Bjorvatn, & Sivertsen, 2014), however, the directionality and potential causality has yet to be sufficiently examined and more targeted interventions are needed (Doufas, 2017).

People with comorbid pain and insomnia has shown a decrease in cognitive abilities and an increase of affective symptoms in healthy subjects (Legrain, Damme, Eccleston, Davis, Seminowicz, & Crombez, 2009). This may contribute to exacerbate each condition because the individual has reduced coping abilities and motivation for treatment. Although more research is needed, non-pharmacological management of sleep may ameliorate pain symptoms in older adults (Vitiello, Rybarczyk, Von Korff, & Stepanski, 2009).

Pain, sleep and BPSD in NH patients with dementia. As mentioned, pain is frequent in people with dementia, as are sleep disturbances. The bidirectional relationship found between pain and sleep in cognitively healthy people may be transferable to people with dementia. Despite this, there are few studies investigating this relationship in people with dementia (Flo et al., 2017). Flo et al. (2017) concludes that there are studies that show associations between pain and sleep in people with dementia, however there are too few and not enough high-quality studies to support and suggest that the bidirectional relationship shown in other populations is equivalent in people with dementia.

A few recent studies have examined the associations between pain and sleep problems in NH patients with dementia. With a stepwise pain medication protocol (Blytt, Bjorvatn, Husebo, & Flo, 2018) found that pain improved sleep after one week of treatment, however there were not significant improvements at 13-weeks long-term follow-up in the same sample (Blytt, Bjorvatn, et al., 2018; Blytt, Husebo, Flo, & Bjorvatn, 2018). This study also illustrates the difficulty in separating the potential bi-directional effects between pain and sleep, and potential effect treatment has on pain or sleep.

Pain is associated with increased BPSD in people with dementia (Buffum, Miaskowski, Sands, & Brod, 2001; Cohen-Mansfield et al., 2015; Husebo et al., 2016). Furthermore, pain has been found to be associated to certain BPSD in people with dementia, with consistent findings for associations between pain and depression and pain and agitation/aggression. There were some findings for association between pain and other BPSD, however the associations was relatively weak (van Dalen-Kok, Pieper, de Waal, Lukas, Husebo, & Achterberg, 2015). The pain-depression dyad has been investigated in people with dementia in a few studies (Cipher & Clifford, 2004; Leong & Nuo, 2007; Malara et al., 2016; Williams, Zimmerman, Sloane, & Reed, 2005), and the associative relationship are suggested

for this population as well, however it is not clearly understood yet (Blytt, Husebo, et al., 2018; Erdal et al., 2017; Husebo, Ballard, Fritze, Sandvik, & Aarsland, 2014).

As the communication abilities of the patient decline, the patient loses their ability to voice their needs. Behaviour, such as vocalizations, facial expressions and body movements may then be the only signs of pain in people with dementia (Flo, Gulla, & Husebo, 2014). Pain may then result in challenging behaviour such as aggression, agitation, mood swings, restlessness, and screaming (Cohen-Mansfield et al., 2015; Husebo et al., 2016). These issues illustrate the challenges related to the clinical assessment of pain in people with dementia.

Treatment of BPSD, Pain and Sleep Problems in NH Patients and People with Dementia

Due to the complexity of BPSD and dementia, there is a need for an individual approach in regard to the symptom management. The high distress these symptoms inflict on patients and caregivers further enhances the need for more adapted treatments for the individuals affected, both directly and indirectly. Interventions, both non-pharmacological and pharmacological, are directed both towards improvement in BPSD in general and/or specific BPSD symptoms.

Firstly, it should be mentioned that several factors are thought to exacerbate BPSD. These include, but are not exclusive to, poor vision and hearing, limited mobility, pain or physical discomfort, incontinence, environmental stressors and language ability in local language. It is always important to assess and treat or correct potential symptoms or other factors that may lead to BPSD (International Psychogeriatric Association, 2012).

Pharmacological treatment of BPSD, sleep and pain. Non-pharmacological interventions are always preferred over pharmacological interventions as first-line treatment. This is due to the risk of substantial adverse events and drug-drug interactions, as older adults with dementia are prone to more serious side-effects of a number of drugs commonly used for

treating BPSD (Kales, Gitlin, & Lyketsos, 2015; Tampi, Tampi, Balachandran, & Srinivasan, 2016).

The strongest evidence for pharmacological treatment of BPSD is for atypical antipsychotics, with small to moderate effects. Other medications used in addressing BPSD symptoms are antidepressants, mood stabilizers, cholinesterase inhibitors and memantine, typical antipsychotics, and benzodiazepines (Kales et al., 2015). Long-term usage of antipsychotics significantly increases mortality compared to placebo (Ballard et al., 2009; Corbett, Burns, & Ballard, 2014), similar findings has been found with antidepressants (Coupland, Dhiman, Morriss, Arthur, Barton, & Hippisley-Cox, 2011), and benzodiazepines (de Gage et al., 2012). In Norwegian NHs there is prevalent use of psychotropic drugs in specialized dementia care units (Halvorsen et al., 2017), in NH patients with BPSD and dementia. Indeed, multiple psychotropic usage was associated with increased neuropsychiatric symptoms (NPS) (Gulla et al., 2016). Despite the lack of evidence of effect of these drugs (Corbett et al., 2014; Gulla et al., 2016), the continued use of multiple psychotropics might reflect the strain put on patients and caregivers by these symptoms, and a belief in the additive effect of drugs (Gulla et al., 2016).

Pharmacological treatments for sleep problems in people with dementia have limited evidence, and many drugs commonly used, including benzodiazepines, non-benzodiazepine hypnotics, and tricyclic antidepressants do not have sufficient evidence for usage in people with dementia (McCleery, Cohen, & Sharpley, 2016).

As mentioned, pharmacological treatment for pain in people with dementia has been increasing and recent studies NH patients with dementia show similar prevalence of pain-relieving medication use in NH patients both with and without dementia (Sandvik et al., 2016; Tan et al., 2016). Targeting pain with a stepwise protocol has been found to have an effect on pain in people with dementia (Sandvik et al., 2014). At the same time, recent research suggest

that opioid treatments (buprenorphine transdermal system) are not tolerated as well as earlier assumed in NH patients with dementia (Erdal, Flo, Aarsland, Selbaek, et al., 2018).

Non-pharmacological treatment of BPSD, sleep and pain. Non-pharmacological interventions include a variety of behavioural, caregiver centred and environmental approaches and focuses mainly on the psychosocial factors around and within the individual to decrease BPSD, sleep and pain.

Patient centred care refers to an umbrella term of treatment and care philosophies that focus on the individual behind the disorder as opposed to focusing on the disorder (dementia) and the negative symptoms associated with the disorder (Høyland et al., 2016). While not dismissing pharmacological treatment, patient centred care focus on psychological aspects related to how people with dementia are experiencing personhood. Particularly how he or she may experience loss of autonomy and empowerment, and how this might influence that individual and their identity (Høyland et al., 2016; Kitwood & Bredin, 1992).

Dementia care mapping is a method based on patient centred care that aims to map to what degree the environment enhances well-being in the persons with dementia in institutions. After observation and analysis the results are shared in a conversational discussion with staff where the aim is to enhance the aspects of the environment that promotes well-being by making staff more aware of the sociopsychological attitudes expressed in dementia care (Rokstad, 2004). Person centred care and dementia care mapping has been shown in studies to significantly reduce agitation (Chenoweth et al., 2009).

The following non-pharmacological treatments show small and moderate consistent effects on improving BPSD and sleep problems in people with dementia and/or cognitive impairment; reminiscence therapy (Woods, O'Philbin, Farrell, Spector, & Orrell, 2018), simulated presence therapy (Abraha et al., 2017), cognitive training and rehabilitation for mild to moderate stages of dementia (Bahar-Fuchs, Martyr, Goh, Sabates, & Clare, 2019),

music therapy (Gerdner, 2000; van der Steen, Smaling, van der Wouden, Bruinsma, Scholten, & Vink, 2018; Zhang et al., 2017), exercise programs (Forbes, Forbes, Blake, Thiessen, & Forbes, 2015) and light therapy (Chiu, H.L. et al., 2017; Forbes, Blake, Thiessen, Peacock, & Hawranik, 2014; Mitolo, Tonon, La Morgia, Testa, Carelli, & Lodi, 2018). Interestingly, some of these treatments, such as music and exercise has also been found to improve pain symptoms in people with dementia (Pedersen & Saltin, 2015; Pongan et al., 2017).

Below follows a focus on light therapy, as this may improve sleep and BPSD, and thus may, through the bidirectional relationship between sleep, mood and pain, also improve pain in people with dementia.

Bright light therapy in nursing home patients and people with dementia. Light therapy is a promising alternative to drugs in treating sleep disturbances and BPSD in people with dementia. Light therapy is an intervention addressing several aspects and perspectives in treating BPSD, such as the physical environment and environmental vulnerability, stimulation and unmet needs as well as targeting specific BPSD, such as depression, sleep disturbances and abnormal circadian patterns. Furthermore, light therapy has low risk of adverse effects and is therefore safer for a vulnerable population such as NH patients and people with dementia.

Bright light therapy (BLT) has been shown in studies with healthy cognitive people to suggest positive effects on a number of symptoms and disorders, including general sleep problems, circadian outcomes, insomnia (van Maanen, Meijer, van Der Heijden, & Oort, 2016) pain in fibromyalgia (Burgess, Park, Ong, Shakoor, Williams, & Burns, 2017) borderline personality disorder (Bromundt, Wirz-Justice, Kyburz, Opwis, Dammann, & Cajochen, 2013) and depression and anxiety in hospitalized patients (Canellas, Mestre, Belber, Frontera, Rey, & Rial, 2016; Kopp et al., 2016; West et al., 2019) to mention a few.

However, there are few studies on BLT with people with dementia. A Cochrane meta-analysis investigating BLT's effect in people with dementia concluded that there was inconclusive evidence for effects (Forbes et al., 2014). A more recent meta-analysis by Chiu, H.L. et al. (2017) found that BLT had significant and moderate effects on sleep quality, behavioural disturbances and depression in people with dementia, mild cognitive impairment and memory dysfunction. Mitolo et al. (2018) report similar results with inconclusive findings, but a positive trend with beneficial effects on sleep and circadian rhythm, cognition, depression, and agitation. However, some studies report a worsening in BPSD symptoms and some report no effect on outcomes, making it hard to conclude in either a positive or negative direction (Mitolo et al., 2018).

There are a number of methodological challenges when studying BLT in NH patients with dementia (van der Ploeg & O'Connor, 2014), and studies vary widely in their designs making it hard to compare studies. For instance participant inclusion might be people with dementia diagnosis as defined by diagnosis manuals (ICD-10 or DSM-V), mild cognitive impairment, only people with AD or even dementia as measured by standardized test (MMSE<20), all which are valid inclusion criteria, but making comparing studies hard (Mitolo et al., 2018). In sum studies vary over a number of aspects; treatment delivery, light intensity, light timing, treatment duration, study duration, and participant characteristics, and most have small sample sizes and high degree of heterogeneity in participants (Chiu, H.L. et al., 2017; Forbes et al., 2014; Mitolo et al., 2018; van der Ploeg & O'Connor, 2014).

BLT may be delivered in a variety of ways, lightboxes, wall and/or ceiling-mounted light fixtures. Traditionally, it is delivered using table-mounted lightboxes, where participants have to sit in front of high intensity (>90 lux) light for approximately 30 minutes. When administering light therapy for NH patients with dementia this causes potential challenges, specifically to treatment adherence and stimulation levels, as this is often experienced as

uncomfortable. Ceiling mounted light fixtures for this reason seems a better treatment intervention method for BLT in NH patients with dementia, as all patients will be exposed at the same time and thus have higher treatment adherence and ensures similar treatment exposure. Further, new LED technology together with ceiling mounted light has the advantage that light exposure can be extended to a longer period of time and expose the participants to similar light as outdoor light, both in colour (kelvin), intensity and duration. This can be programmed ensuring that all light in all treatment conditions are constant and identical.

Aims and hypotheses

This thesis aims to investigate pain in a sample of NH patients with dementia. In particular, this thesis aims to investigate the association between pain sleep and BPSD, and whether BLT affects pain over time. A number of aspects are known to influence pain, BPSD and sleep in people with dementia and the thesis will also investigate how drug usage (overall drug use and psychotropic drug use), and the demographic variables age and sex are correlated with pain.

The primary hypothesis in this thesis is that BLT will have an effect on pain. Pain is bidirectionally linked with sleep and other BPSD (in particular agitation and depression) and BLT might therefore affect pain in this sample.

This thesis also hypothesizes that there is an association between pain and: sleep, agitation, depression and the presence of BPSD in general at baseline.

Method

Trial Design

This thesis used data from the DEM.LIGHT trial (Therapy Light Rooms for Improved Sleep in Dementia Patients) which was a cluster, randomized placebo-controlled trial (RCT)

investigating bright light therapy influence on several variables in NH patients with dementia (the DEM.LIGHT trial, ClinicalTrials.gov Identifier: NCT03357328). The trial was conducted in specialized long-term dementia care units in NHs in the Bergen municipality, Norway from September 2017 to April 2018. The Department of Health and Care, City of Bergen was invited to participate with a total of 78 patients in eight eligible NH dementia units (meaning that they did not participate in other trials or projects, and that layout was suitable for light instalment). NH dementia units were randomized to either the intervention group (4 units) or the control condition (4 units).

Sampling Procedures and Randomisation

Together with the staff at the NH units the researchers screened NH patients for eligibility and evaluated the ability to give written informed consent for participation in the trial. See Table 1 for inclusion and exclusion criteria for participants in the trial.

Table 1: *Inclusion and exclusion criteria for participants*

Participants were included if they were:	Participants were excluded if they were:
≥60 years and in long-term care facilities (> 4 weeks)	blind or otherwise could not benefit from bright light therapy (BLT)
had dementia according to DSM – V	participated in different trial
had either sleep/circadian rhythm disruption, BPSD as identified by NPI-NH or severely reduced ADL-function	had a condition contra-indicated for the intervention
could provide written informed consent or if the participant did not have this capacity, a written proxy informed consent from a legal authorized representative	had an advanced or severe medical disease and/or expected survival less than 6 months or other aspects that could interfere with participation
	were psychotic or had other severe mental illness

Note. DSM-V=Diagnostic and statistical manual of mental disorders fifth edition, BPSD=Behavioural and psychological symptoms of dementia, NPI-NH=Neuropsychiatric Inventory Nursing home edition, ADL=Activites of daily living.

When a participant at any one moment fulfilled an exclusion criteria or experienced adverse effects by the intervention no further assessment was recorded. The light in the NH units was installed in such a manner that it was possible for single patients to avoid these and still be in social common areas.

The trial was randomized at cluster level (NH units). There were no crossover of NH staff between the NH units, ensuring no contamination between the control and intervention condition.

Intervention

Ceiling-mounted LED-lights were used as treatment delivery method. The intervention group received light varying in intensity (lux) and colour temperature (Kelvin) during the day. The lights were installed in the living rooms of the NH units. Between 07:00 and 10:00 light was provided at 400 lux at eye level, with 4000 K (warm white). Between 10:00 and 15:00 the light was provided at 1000 lux at eye level, with 6000 K (cold white). From 15:00 to 18:00 the light returned to the morning condition. When the light was turned on from 18:00 to 07:00, it was standard light (about 100 lux at eye level, 3000K). The control group received standard light (100 lux at eye level, 3000K). The light was administered between 07:00 and 18:00; and the same when light was turned on between 18:00 to 07:00. The trial was conducted during the winter season in order to ensure similar light levels in all NH units.

The DEM.LIGHT trial asked the NH staff to note the time each participant was in the living room area.

Measurements

The data for outcomes or predictors used in this thesis are from the DEM.LIGHT trial These are data collected from people with moderate to severe dementia. Assessment scales are

therefore mostly proxy-rater scales. Below follows a detailed description of the ones used in this thesis.

Exposure to light was assessed by asking the nurses performing the proxy-rating to note the general amount of time a NH patient spent in the livingroom where the intervention light was delivered.

Drug use was registered for each participant. Total number of regular drugs and psychotropic drug use were based on prescription in medical record at baseline. Psychotropic drugs are included in total number of drugs. Drugs on demand was not included.

Mobilization – Observation – Behaviour – Intensity – Dementia 2 (MOBID-2) pain scale is a staff-administered pain assessment tool for patients with advanced dementia. The scale is comprised in two parts, in pain location and intensity measurement. Part 1 measures pain intensity inferred from the patient's behaviour during standardized, guided movements, and part 2 measures pain behaviours related to location; internal organs, head and skin. Total score ranges from 0 to 10, where 10 is worst possible pain. The cut-off for clinically relevant pain is ≥3. The assessment tool has good reliability, validity and responsiveness. (Husebo, Ostelo, & Strand, 2014; Husebo et al., 2007).

Mini Mental State Examination (MMSE) is a cognitive functioning screening tool which describes severity of cognitive impairment in 11 domains (registration, orientation to time and place, short-term recall, attention, calculation, long-term recall, naming, repetition, comprehension (verbal and written), writing, and visuospatial construction). With 30 items this results in a total score between 0-30: 0-10=severe impairment, 11-20=moderate, 21-25=mild, and 26-30=no impairment. The cut-off for clinically relevant cognitive impairment is ≤25. MMSE has good reliability and validity (Folstein, Folstein, & McHugh, 1975).

Neuropsychiatric Inventory – Nursing Home version (NPI-NH) is a proxy-rater instrument for measuring frequency and severity of 12 neuropsychiatric items people with

dementia (Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein, 1994). These are delusions, hallucinations, agitation/aggression, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behaviours, nighttime behaviour/sleep, and appetite and eating disturbances. Frequency (0-4) times severity (1-3) resulting in a composite score of each item of 0 = not present and 12=most frequent and severe symptoms. Clinically significant cut-off ≥4 for each symptom and total sum score scale 0-144. The Norwegian version of the NPI-NH has good validity and reliability (Selbaek, Kirkevold, Sommer, & Engedal, 2008).

Sleep Disorders Inventory (SDI) is an expanded proxy-rater inventory derived from the NPI-NH and consists of the seven sub-questions of the sleep disturbance item making the scale seven items all in all. Each question is measured with frequency, severity and caregiver distress during the last two weeks. Frequency ratings range from 0=not present to 4=once or more per day (every night). Severity ratings range from 0=not present to 3=marked. Caregiver distress rating range from 0=not at all to 5=very severely/extremely. Caregiver distress is not part of the SDI total score sleep on seven symptoms. The SDI total score is the average from the frequency scores times the average of the severity scores (Tractenberg et al., 2003). The inventory has good validity and reliability in a population of people with dementia (Tractenberg et al., 2003).

Cornell Scale of Depression in Dementia (CSDD) is a proxy-rater instrument for measuring depression in people with dementia (Alexopoulos, Abrams, Young, & Shamoian, 1988). The instrument measures depression in 5 domains; mood-related signs, behavioural disturbance, physical signs, cyclic function, and ideational disturbance during the last week. When used the rater scores 19 items on a scale from; 0=no symptoms to 2= severe, or "a" which refers to "not possible to score". Total score ranges from 0 to 38. Clinically relevant sum score cut-off is ≥8= depression, and >12= moderate to severe depression. The instrument

has good interrater reliability and validity in a population of people with dementia (Kørner et al., 2006).

Cohen-Mansfield Agitation Inventory (CMAI) is a proxy-rated instrument measuring 29 agitation symptoms. The symptoms are pacing, inappropriate robing or disrobing, constant requests for attention, punching, making strange noises, screaming, scratching, trying to get to a different place, general restlessness, complaining, negativism, handling things inappropriately, hiding things, hoarding things, tearing things, performing repetitious mannerisms, verbal sexual advances, physical sexual advances, intentional falling, throwing things, biting, eating, inappropriate substances and hurting oneself or other. Each item is rated in frequency on a scale from 1=never to 7=several times in an hour, total score range is 29–203. The scale has with good validity and reliability (Cohen-mansfield, Marx, & Rosenthal, 1989).

The primary outcome in the DEM.LIGHT trial were sleep and BPSD and the trial was designed for these outcomes. This thesis uses the measurement of pain, MOBID-2, which was a secondary outcome.

Statistical Analyses

A researcher at the DEM.LIGHT trial conducted analyses of systematic differences at cluster level. No systematic differences at cluster-level were detected and cluster was not added to the model.

All analyses were made using IBM SPSS Statistics 25 for Windows. Demographic and baseline patient characteristics were computed with descriptive exploratory statistics. Bivariate correlations were conducted between pain assessment (MOBID-2) scores at baseline and the following variables: sleep problems (SDI) scores at baseline, cognitive functioning (MMSE) at baseline, agitation symptoms (CMAI) at baseline, depression symptoms (CSDD)

at baseline, BPSD symptoms (NPI-NH) total scores at baseline, specific BPSD (NPI-NH) symptoms, total medicine usage and psychotropic medicine usage.

A linear mixed model (LMM) analysis for repeated measures was performed in order to fully use all available data, as there was a substantial amount of missing data. The LMM was conducted to assess within-subject's differences over MOBID-2 scores over time, and between-group differences in MOBID-2 based on the BLT intervention. In general, the participants were in the living room in midday, when the light had the strongest non-visual effects (cold blue light with high intensity). The variable "time spent in the living-area", denoting exposure to light, had no effect on the model and was not included in the final analyses, suggesting that the differences in light exposure within the intervention group was without significance. Thus, this variable was not entered in the LMM. The variable "cluster" (i.e., nursing home units) was not entered for the same reason. Included in the LMM were the following fixed effects: time (MOBID-2 baseline, MOBID-2 at week 16 and MOBID-2 at week 24), intervention (intervention vs control group) and interaction between the two (time*intervention). In addition, the following variables were added to the model one by one (alone) to assess whether to keep them in the final model: sex, age, cognitive impairment (MMSE), depression (CSDD), sleep disturbances (SDI), agitation (CMAI), neuropsychiatric symptoms (NPI-NH) in total and for each specific neuropsychiatric symptom, number of drugs in total (med) and number of psychotropic drugs (Nmed). The variables which were significant in these models (agitation, depression, Neuropsychiatric symptoms and number of psychotropic drugs) were kept in the final model, together with time, intervention and time*intervention. The reason for this procedure was that adding all the predictors to the model would result in a too high number of predictors for the sample size (i.e. low statistical power). Participant was included as a random effect. Restricted measures of maximum likelihood (REML) was used as the estimation method.

Ethical Aspects

Together with the physicians at each NH, patients likely to provide informed consent were identified. The researchers gave information about the study in an adapted way to eligible patients and continuously evaluated if the patient was able to provide consent, where most patients were not able to. For these patients the authorized legal guardian of the patient was directly contacted by phone. The guardian was given a letter in the mail containing all relevant information (aims, proceedings, and ethical approval) so that they could give presumed informed consent by proxy for the patient. In a presumed consent the guardian is asked to consider what the patient would wish in the given situation, not what they believe to be best. Patients that expressed discomfort or protests during the study period was understood as withdrawing their consent. The trial was approved by the Regional Ethics Committee (REC South East 2016/2246) and is registered at Clinicaltrials.gov (Trial number NCT03357328).

Role of Student Author

The data was accessed with permission from Associate professor Elisabeth Flo, Department of Clinical Psychology, Faculty of Psychology. The author was not involved in data collection. The author had a significant and primary role in the planning, data analysis and interpretation of the results. The author has written the entire manuscript with supervision from Flo and co-supervisor Thun.

Results

A total of 78 NH patients with dementia were assessed for potential participation in the trial, resulting in 69 NH patients with dementia across 8 NH units were included in the trial. See Figure 2 for flow-diagram of participant sampling and assignment to intervention or comparison group. One participant from the intervention group was excluded from the analyses due to high cognitive functioning (MMSE=29). Patient characteristics at baseline are presented in table 2.

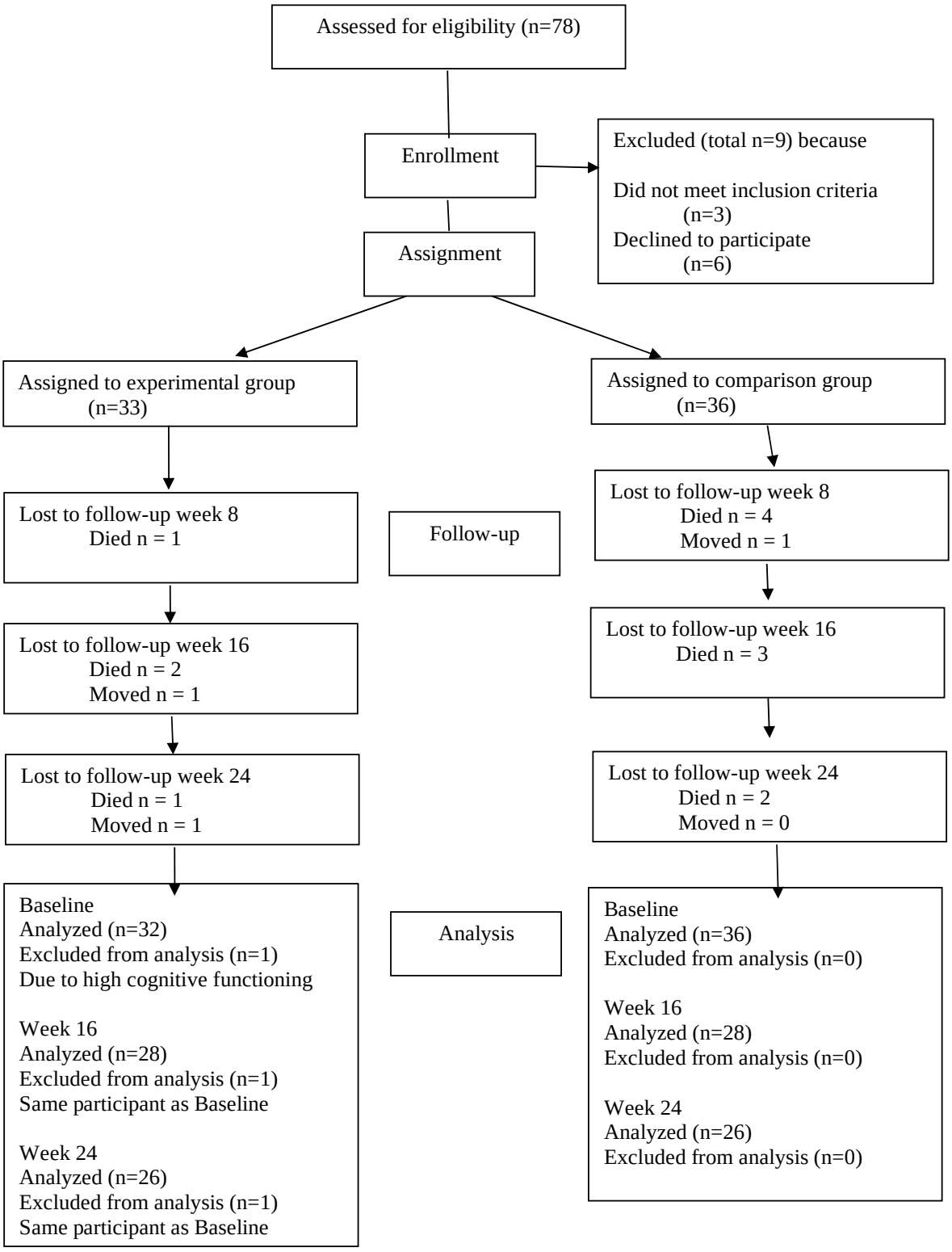


Figure 2. *Flow-chart of participant inclusion and treatment assignment*

Table 2. *Demographic and clinical characteristics of participants*

	Total (n=68)	N
Age (y)	83.6 ± 7.2	68
MOBID-2	2.6 ± 2.0	65
MOBID-2 score ≥ 3	34 (52%)	65
SDI frequency	5.5 ± 6.1	65
SDI score ≥5	25 (38%)	65
MMSE	5.8 ± 5.7	59
MMSE score ≤10 (severe dementia)	48 (81%)	59
CSDD	9.1 ± 6.1	68
CSDD score ≥8	37 (54%)	68
NPI-NH total	25.7 ± 23.0	68
CMAI	48.0 ±14.4	68

Note. Numbers are mean ± standard deviation or number of patients (percentages). *N* number of participants completed data. (n-missing). *MOBID-2* Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, *SDI* Sleep Disorder Inventory, *MMSE* Mini-Mental State Examination, *CSDD* Cornell Scale for Depression in Dementia, *NPI-NH* Neuropsychiatric Inventory-Nursing Home Edition, *CMAI* Cohen-Mansfield Agitation Inventory.

As shown in Table 3, there were no significant correlations found between pain (MOBID-2) and the following variables: sleep problems (SDI), cognitive impairment (MMSE) and agitation (CMAI). Positive correlations were found between pain measurements and the following variables: depression (CSDD), BPSD (NPI-total), delusions (NPI-NH), disinhibition (NPI-NH), total drug use and psychotropic drug use.

A negative correlation was found between pain measurement and elation (NPI-NH).

Table 3. *Pearson Coefficients (r) for bivariate correlation analyses between pain (MOBID-2) and cognitive function, sleep, agitation, depression, and other behavioural and psychological symptoms of dementia, and drug use at baseline*

	MOBID-2	N
MMSE	.689	59
SDI	.027	62
CMAI	.221	65
CSDD	.391**	65
NPI-NH_Total	.266*	65
NPI-NH_Delusions	.307*	65
NPI-NH_Elation	-.279*	65
NPI-NH_Disinhibition	.299*	65
Drug total (Med)	.294*	65
Drug psychotropic (Nmed)	.261*	65

Note. *$p<.05$, two-tailed. **$p<.01$, two-tailed. *MOBID-2* Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, *SDI* Sleep Disorder Inventory, *MMSE* Mini-Mental State Examination, *CSDD* Cornell Scale for Depression in Dementia, *NPI-NH* Neuropsychiatric Inventory-Nursing Home Edition, *CMAI* Cohen-Mansfield Agitation Inventory.

The results from the LMM analysis showed that there was no significant effect of intervention on pain assessment. There was no significance of time on pain assessment, and no interaction effect between the two fixed effects. There was a significant effect of depression scores on pain measurements, were higher depression scores predicted higher pain assessment scores. There were no significant results of any of the other fixed effects in the final model. The results are presented in Table 4.

Table 4. *Linear mixed model analysis with dependent variable pain assessment (MOBID-2)*

		Estimates (β)	t-value (SE)	p	95% CI [LB, UB]
Fixed effects	Intercept	1.11	1.69 (.66)	.093	[-.19, 2.41]
	Intervention	-.70	-1.70 (.41)	.090	[-1.51, .11]
	Time	-.10	-.42 (.24)	.677	[-.58, .38]
	Intervention*time	.07	.20 (.34)	.840	[-.61, .75]
	Nmed	.11	.97 (.12)	.333	[-.12, .34]
	CSDD	.12	3.28 (.04)	.001*	[.05, .19]
	NPI-NH total	.01	.65 (.01)	.514	[-.02, .03]
	CMAI	.00	.21 (.02)	.834	[-.03, .03]

Note. Dependent variable MOBID-2_total. *$p<.01$, two-tailed. *CI* Confidence interval, *LB* Lower Bound, *UB* Upper Bound. *Nmed* psychotropic drug use. *CSDD* Cornell Scale for Depression in Dementia, *NPI-NH* Neuropsychiatric Inventory-Nursing Home Edition, *CMAI* Cohen-Mansfield Agitation Inventory.

Discussion

The objective of this thesis was to investigate the association between pain, sleep and BPSD, and to test whether BLT affected pain over time. The results showed that BLT did not have a significant effect on pain, and the primary hypothesis was not confirmed. However, depression had a significant predictive effect of pain and was positively correlated with pain at baseline.

Further, positive correlations were found between pain and prevalence of BPSD in general (total NPI-NH). Surprisingly, there was also positive correlations between pain and delusions, and disinhibition, and a negative correlation between pain and elation. Positive correlations were found between pain and overall drug use, and pain and psychotropic drug use.

There was no significant correlation between pain and the following; agitation, sleep, or cognitive impairment.

In sum, the primary hypothesis was not confirmed, however our hypotheses that pain was related to the presence of BPSD in general and depression was confirmed.

Methodologic Issues

The methodological choices and study design contribute to either enhancing or decreasing internal and/or external validity. Internal validity refers to whether or not the results are correct and valid for the sample investigated (Pripp, 2018), and is central in estimating the quality of a RCT. External validity refers to in what degree the results of a trial are generalizable to the clinical population examined (Akobeng, 2008; Rothwell, 2005). There are two categories of errors that can occur in research: random error and systematic error. While random errors vary unpredictably from measurement to measurement, the systematic errors affect measurements the same amount or by the same proportion. An RCT design is thought to deal with some of the most common systematic errors, but it is not possible to avoid them completely. Thus, it is important to be aware of potential systematic errors and the limitations that such errors impose on the study results and subsequent interpretations. Clinical trials have four main sources for systematic errors of internal validity; selection bias, performance bias, detection bias and attrition bias (Akobeng, 2008). Selection bias refers to differences in the groups due to their group assignment. Performance bias refers to when there are systematic differences in exposure factors that could influence outcome between the groups. Detection bias refers to how assessment was done, in particular in subjective outcomes. Attrition bias refers to the systematic differences in groups based on loss or withdrawal of participants (Akobeng, 2008). In this section I will look at the strengths and limitations of the present study that affect the internal and external validity, and thus how the results may be interpreted.

Trial design. This was a RCT, which is considered the most powerful experimental study design in quantitative research (Stolberg, Norman, & Trop, 2004) due to its ability to

control the participants exposure to the experimental intervention. However, some aspects are lost in such quantitative design, and qualitative interviews were conducted in the DEM.LIGHT trial, inviting NH staff to reflect upon how the BLT was experienced and how they thought the patients responded to the light. The reporting of the qualitative data was unfortunately beyond the scope of this thesis.

Trial setting. The trial was conducted in specialized dementia care units, and external validity was kept as the trial setting was as similar to the natural setting as possible. Some changes were made with the installation of light fixtures. These were ceiling-mounted and were considered as being minimally invasive.

Sampling. A convenience sample at cluster level comprised the trial. This may decrease the likelihood of inclusion for the target population and increases the potential of sampling bias (Thompson, 1999). Notably the only aspects differing the NH units included in the trial from others were that they did not participate in another trial and that they did not have limitations in layout regarding instalment of the light fixtures (for example preservation restrictions).

Recruitment and sample characteristics. Participants in this trial was recruited based on wide inclusion criteria, including all patients in a dementia unit showing a probable dementia diagnosis (MMSE or diagnostic criteria) and symptoms of either sleep disturbance, BPSD or decreased functionality of activities of daily living (ADL). These inclusion criteria reflect the NH population with dementia well, and indeed only 3 participants out of 78 NH patients were excluded due to not meeting inclusion criteria. It is safe to assume that the sample is representative for the population of NH patients in long-term care, in particular specialized dementia units. This enhances external validity. Meanwhile, this inclusive recruitment strategy meant that the sample showed a high degree of heterogeneity. This is seen in large SD in demographic and participants characteristics at baseline (see Table 2.).

This could have affected the results, and potentially the internal validity of this study (see also the statistical section regarding power analyses).

Adherence to treatment and variability in light exposure. The trial intervention was BLT administered by installed LED light fixtures in the ceiling in the living rooms of the NH units, and these were programmed on a 24-hour cycle (please see the method section for details regarding light intensity and temperature). This form of light administration increases treatment adherence and implementation as compared to traditional BLT light boxes. As long as the participant was in the living room he or she was exposed to the intervention. The DEM.LIGHT study asked the nurses to note the time each NH patient spent in the living room area. The patients generally spent their time in the living room area early to late afternoon, i.e. the time the light had the strongest non-image forming function effect. The variable "exposure time" had no effect on the model and was not included in the final analyses, suggesting that the difference in light exposure within the intervention group was not noteworthy. This reduces the risk of performance bias and strengthens the internal validity of the study. This also increases the applicability and feasibility of this type of BLT.

Outcomes. Data was collected using the proxy-rater scales CSDD, MOBID-2, CMAI, SDI and NPI-NH. As mentioned, a proxy-rater is a person that fills out structured assessment scales on behalf of another person, based on observations in behaviour and vocalisations by that person (Corbett et al., 2012). This method is used when participants are not able to respond accurately themselves (Husebo, Ostelo, et al., 2014). When using proxy-raters there is an increased risk of information and recall bias. Information bias refers to the possibility that the rater gives incorrect information, either consciously or unconsciously (Althubaiti, 2016). Furthermore, the rater's personality or mood may influence the assessment (Snow, Cook, Lin, Morgan, & Magaziner, 2005). Meanwhile, in this study only measurements scales that have been shown to have good psychometric properties were used, and most have been

validated in the population. The proxy-raters got training and were supervised by researchers with clinical experience throughout the data collection period. This ensured that the data collection was done in adherence with the recommended administration of these instruments.

Proxy-rating of symptoms may be particularly challenging when asking day shift staff about the patients sleep. In this instance, the quality of data depends on the night shift staff to convey info to day shift staff as reliably as possible to avoid information bias. Researchers from the DEM.LIGHT trial has validated the Sleep Disorders Inventory (SDI) to Norwegian and in a NH population with dementia using the day staff's responses (Tractenberg et al., 2003).

In this study, the correct use of measurements scales that have been shown to have good psychometric properties, as well as being validated in the population studied decreases the possibility of information and recall bias.

Randomization and blinding. This trial was successfully randomized which controls for selection bias, making the intervention group and control group similar, and potential treatments effects are then due to the treatment. Nevertheless, despite proper randomization, the two groups are relatively small and significant differences between the intervention and control group may happen by chance. In addition, the randomization was done at cluster level (i.e. NH unit). It is possible that there are systematic differences at cluster-level, although this was not detected in our sample. The successful randomization strengthens the internal validity.

The trial included a control condition, and although the placebo/nocebo effect should not interfere in people with severe dementia the same way as in people with intact cognition, the knowledge of treatment assignment might affect the staff at the NH units. Any changes in care practices or staff behaviour could significantly influence the patients, making a control condition necessary (Hawe, Shiell, & Riley, 2004; Squires et al., 2015). NH staff at each NH

unit was blinded in regard to allocation to either intervention or control condition. Indeed, blinding health personnel had a significant influence on treatment effects in the studies examined in the meta-analysis by Chiu, H.L. et al. (2017). The control condition entailed changing the light, but only to standard indoor lighting. Thus, the control condition also ensured that all control units had a constant and similar light further increasing internal validity through the increased control of the compared control condition. It should be noted that staff with particular knowledge on light treatment could potentially guess the group allocation.

Statistical power and sample size. Based on power analyses, the initial preferred sample size was 80 participants (controlling for attrition). However, due to smaller units than anticipated, the initial number of NH patients decreased to 78, resulting in 69 participants at baseline. In addition, because pain was not the primary outcome of this trial, the power analysis was not performed with the MOBID-2 as an outcome measure. This may impact the statistical power.

The sample size is relatively small compared to standard RCTs, thus making assumptions and interpretations of the results with less statistical power. However, compared to other studies investigating light therapy in people with cognitive impairment or dementia, the sample is relatively big (Forbes et al., 2014). Studies with larger samples might have better statistical power of finding treatment effects with the same treatment, and an effect of BLT on pain cannot be disregarded. Furthermore, the sample in the DEM.LIGHT trial show more variation in types of dementia and degree of dementia compared to previous research. The power analyses for estimating sample size was based on these previous studies with healthier participants. Drop-out and noise in the data in this sample may have required a larger sample size to show significant effects.

Attrition. The two groups had similar drop-out rates as shown in Figure 2, and these were quite limited with a few participants lost to each follow-up measurements. There were no reports of discomfort or withdrawal of consent due to the intervention. All drop-out cases were either due to death or moving, which is common in the NH population (Statistics Norway, 2019) and further supports the assumption that the sample is representative for nursing home patients with dementia.

Choice of statistical analysis – dealing with missing data. The main analyses of BLT intervention on pain were done using an LMM analysis. This was appropriate due to a substantial amount of missing data in the outcome measure of pain measurements (MOBID-2). Compared to a mixed model ANOVA, which is commonly used as analysis for repeated measures designs, the LMM analysis allows for retaining data for subjects that have missing data for one or more variables (Bennett, 2001). The assumption for the LMM is that the data are missing at random (Heck, Thomas, & Tabata, 2013), and a Raw Maximum Likelihood (REML) method where all available data about the observations are used to generate estimates of missing based on maximum-likelihood. This is a suitable method for dealing with missing data in observational data in a clinical sample (Bennett, 2001). The use of the LMM analysis keeps all available data for the sample and thus strengthening external validity by minimizing reduced sample responses.

Interpretation of the Results

Inconsistent with the primary hypothesis, there was no effect of BLT on pain. Nevertheless, the sample of this study was relatively small, and it is possible that an effect of light on pain can be found in a larger, and perhaps also in a healthier population. Mitolo et al. (2018) suggests that BLT might have more probability of improving symptoms in people with mild to moderate AD. This sample had multiple types of dementia diagnosis and had on average severe dementia as measured by a standardized interview (MMSE), and this could have

influenced the effect of the BLT. In addition, this population was not recruited based on their pain diagnosis, and about half of the population had pain (MOBID-2>3). This means that only half of the population had the potential to improve their pain. Notably, the DEM.LIGHT study has yet to publish results on the effect of BLT on sleep and BPSD, including depression. If the study does not find any effect on these outcomes, it is to be expected that BLT did not have an effect on pain either. Unfortunately, these outcomes are currently under analyses and to be published by other researchers in the DEM.LIGHT research group. These outcomes were thus not possible to report in this thesis. Research investigating the effect of BLT in NH patients with dementia should include pain as an outcome due to the strong associative relationship found between pain and variables improved by BLT in other studies.

There was no relationship found between pain and sleep disturbances in this sample of NH patients with dementia. This is inconsistent with previous finding, as pain and sleep have been associated in a number of studies in people with dementia (Flo et al., 2017). The nature of this relationship is still unknown, and a study found significant improvements in sleep measures due to targeted analgesics, however there was not affect at long-term follow-up in the same sample (Blytt, Bjorvatn, et al., 2018; Blytt, Husebo, et al., 2018). Other symptoms, such as depression and other mood disorders have been found to influence this relationship (Doufas, 2017).

There was no relationship found between pain and agitation, this is inconsistent with previous research (van Dalen-Kok et al., 2015) were pain has been postulated to be a trigger for agitation and aggressive behaviours (Corbett et al., 2014; Husebo, Ballard, & Aarsland, 2011). However, the relationship has not been consistently found in all studies. In the review by van Dalen-Kok et al. (2015) they found relationships between pain and agitation in 5 out of 8 articles with one negative correlation. Some of the studies in the review also reported an association between depression and agitation, and not pain. Further many of the associations

were weak, and the authors suggest a lack of suitable assessment where many of the studies did not use assessments developed for use in people with dementia (van Dalen-Kok et al., 2015).

Further, there was a correlation between pain and other BPSD; the presence of BPSD in general, delusions, disinhibition and elation. This suggests that increased pain is associated with increased symptoms of delusions, disinhibition and BPSD in general. The BPSD symptom elation was negatively correlated with pain at baseline, suggesting that experiencing pain is related to lower elation symptoms or vice versa with high elation symptom related to less pain. These associations are interesting as these symptoms have not been found consistently in previous research (van Dalen-Kok et al., 2015). It is possible that the proxy-raters interpreted the elation symptom as an opposite to depression, in which case the significance and direction of the association between pain an elation is logical.

There was no correlation found between pain and cognitive impairment, sex and age, suggesting that there was no known association between pain and these variables in this sample. However, it seems pertinent to include demographic and essential participant characteristics, as cognitive impairment is such a prevalent symptom in NH patients it seems justifiable to include in the analysis. Notably, when there has previously been found an association between cognitive impairment and pain, the pain tool has often either been self-report or not suitable for people with dementia (Lukas et al., 2013).

The positive correlation between pain and overall and psychotropic drug use is interesting, there are to the knowledge of the author no studies that has investigated specifically the association between pain and psychotropic drug use. It may be that pain-related behaviours and symptoms are interpreted as BPSD and are then treated pharmacologically. This in line with the concern that NH patients with pain do not necessarily receive adequate and targeted treatment (Husebo et al., 2016). Further, another possibility

may be that NH patients with dementia with pain may develop for example depression or sleep problems, and that these symptoms are then treated with antidepressants and hypnotics.

Depression and pain in NH patients with dementia. Depression was found to have a significant effect on pain. This suggests that pain is linked to depressive symptoms in this sample of NH patients with dementia. This is in accordance with the pain-depression dyad found in people with dementia in previous research (Erdal et al., 2017; Leong & Nuo, 2007; van Dalen-Kok et al., 2015). The directionality and causality of this pain-depression relationship is still unknown (IsHak et al., 2018; Li & Peng, 2017). Meanwhile, several studies postulates that decreased pain may improve depression, also in NH patients with dementia (Cipher & Clifford, 2004; Leong & Nuo, 2007). However, as mentioned earlier the research on targeted pain medications (analgesics) for improving depression in NH patients with dementia is not conclusive. Husebo, Ballard, et al. (2014) found improvements in mood disorders, including depression, after pain treatment in NH patients with dementia, however Erdal, Flo, Aarsland, Ballard, Slettebo, and Husebo (2018) found no effect of analgesic treatment on depression. Furthermore, Erdal, Flo, Aarsland, Selbaek, et al. (2018) found that the participants had an increased risk of experiencing adverse events in response to the opioid-based analgesics.

Studies have found effect of BLT on depressive symptoms in people with cognitive impairment or dementia. (Chiu, H.L. et al., 2017). BLT may still be beneficial for influencing pain, as it may improve depressive symptoms in people with dementia, as well as sleep quality.

The studies investigating pain-depression dyad in people with dementia has primarily focused on reducing depressive symptoms through treating pain, however the pain-depression dyad is assumed to be reciprocal (Bair et al., 2003). A number of aspects of depression in NH patients with dementia may influence pain.

NH patients with dementia often have limited communicative abilities and depression may further inhibit the motivation to express the need for help and so pain may not be detected in NH patients with dementia with depressive symptoms until a more standardized assessment is used, as is the case in this trial. The MOBID-2 assessment scale measures, among other, facial expressions to evaluate the pain experienced. In persons with major depressive disorder, pain is linked to an increased reaction in facial expressions than in non-depressed (Lautenbacher, Bär, Eisold, & Kunz, 2017), and this may help NH staff detect pain when using the MOBID-2 scale for pain assessment.

Activity restriction is activity restricted by experienced pain, and has a been suggested as a possible mediator of depressive symptoms in NH patients (López-Lopez, González, Alonso-Fernández, Cuidad, & Matías, 2014). It is possible that depression may further enhance the tendency of inactivity in NH patients with dementia, as inactivity is highly prevalent in NH patients (Neikrug & Ancoli-Israel, 2010) and a common symptom of depression (American Psychiatric Association, 2013). For instance, inactivity could increase pain by increased strain on joints due to muscle atrophy or pressure ulcers not freed from pressure due the patient being in bed or sitting the whole day.

Certain cognitive-behavioural factors have been found to influence the experience and coping mechanisms of pain. A study found that cognitive-behavioural factors, particularly catastrophizing, significantly influence the pain-depression relationship in older adults (Reme, 2016; Wood, Nicholas, Blyth, Asghari, & Gibson, 2016), and cognitive-behavioural interventions has been found to have effect in long term care patients with both pain and depression symptoms (Cipher, Clifford, & Roper, 2007). However, this perspective has not been investigated (to the knowledge of the author) in NH patient with cognitive impairment or dementia. People with dementia may not engage in as much catastrophizing thinking,

however self-efficacy and belief in own abilities to cope with pain may be severely diminished.

There is a dearth of research investigating the pain-depression dyad in NH patients with dementia, and there is a high need for more research. Pharmacological interventions are associated to adverse events and has low to no effect on depression, more research with non-pharmacological interventions are advised.

Ethical Aspects

All data used in this thesis are from the DEM.LIGHT trial, which was conducted in accordance with the Declaration of Helsinki (General Assembly of the World Medical Association, 2014). The data was approved by the Regional Committees for Medical and Health Research Ethics (REC South East 2016/2246), and was registered in a clinical trial database www.clinicaltrials.gov (Trial number NCT03357328) prior to participant enrolment.

Regarding participation in the trial, consent was provided either by the participant or their authorized legal guardian, see method section for a more elaborate account of this.

In accordance with the Declaration of Helsinki (General Assembly of the World Medical Association, 2014) during the study period, the researchers treated expressions of discomfort or protests from participants as withdrawal of consent. Incidentally, no drop-out was recorded due to withdrawal of consent or adverse events. Thus, BLT continues to be a promising non-pharmacological and non-invasive intervention in NH patients with dementia.

Conclusion

The results in this thesis suggest a relationship between pain and depression in NH patients with dementia. Depression was a predictor of pain over time, and there was a significant baseline correlation between pain and depression. The results from this thesis support the pain-depression dyad found in other studies in NH patients with dementia.

There was no effect of BLT on pain, and there was no relationship between pain and sleep, and agitation. Interestingly, there was a significant relationship between pain and delusions, disinhibition and elation, which has not been consistently found in previous research. There was an association between pain and overall drug use, and psychotropic drug use. The positive correlation between pain and drug use, overall and psychotropic, is interesting. It is possible that pain-related behaviours are mistakenly treated with psychotropics. This in line with the clinical concern that NH patients with pain do not necessarily receive adequate treatment.

The lack of an association between pain and sleep is surprising. However, the sample from this study was not primarily participants with clinically relevant pain, and studies should investigate this relationship in NH patient with dementia using pain and sleep as primary outcomes. A suggestion for future research would be to conduct research with BLT targeting people with dementia who also suffer from pain and/or depression. More research is needed in examining the pain-depression dyad in NH patients with dementia, and with non-pharmacological interventions targeting depression and pain.

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