The relationship between psychosis symptoms and pain in nursing home residents

Torstein Frugård Habiger

Thesis for the degree of Philosophiae Doctor (PhD)
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“Arriving at one goal is the starting point to another.”

John Dewey

Scientific environment

This PhD thesis was completed at the Centre for Elderly Care and Nursing Home Medicine (SEFAS), Department of Global Public Health and Primary Care (IGS), Faculty of Medicine, University of Bergen (UiB), and within the Medical Students Research Program at the Faculty of Medicine, UiB. At IGS I attended the Research School in Public Health and Primary Health Care. I started my research career as a part of the Medical Students Research Program (MSRP) and joined SEFAS in 2014. SEFAS is located at the IGS and aims to further excellent research and innovation within nursing home medicine and elderly care. The center was founded and is led by Professor Bettina S. Husebo. My PhD project was funded by UiB, and the COSMOS-trial was funded by the Research Council of Norway (RCN), Rebekka Ege Hegermanns Foundation, and the UiB.

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I have attended various PhD courses on statistical analysis based on the Statistical Package for Social Sciences held by the University of Oslo, as well as several courses on the STATA statistical software package at UiB. I have also attended the Norwegian Research School in General Practice concerning randomized controlled trials in General Practice. At UiB, I have attended the Basic Course in Medical and Health Related research and a course in Good Clinical Practice in clinical research.

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Contents

List of Abbreviations

ACI	Acetylcholinesterase-inhibitors
AD	Alzheimer's disease
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical index
BPSD	Behavioral and Psychological Symptoms of Dementia
COSMOS	Communication, Systematic pain assessment and treatment, Medication review, Organization of activities, Safety
CSDD	Cornell Scale for Depression in Dementia
DLB	Dementia with Lewy-Bodies
FAST	Functional Assessment Staging
IGS	Department of Global Public Health and Primary Care
MOBID-2	Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale 2
MMSE	Mini Mental State Examination
MSRP	Medical Students Research Program
NH	Nursing Homes
NPI-NH	Neuropsychiatric Inventory – Nursing Home version
NPS	Neuropsychiatric Symptoms
NRS	Numerical Rating Scale
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
QoL	Quality of Life
RCT	Randomized Controlled Trial
SEFAS	Center for Nursing Home medicine and Elderly care
SPSS	Statistical Package for Social Sciences
SPTP	Stepwise Protocol for Treating Pain
UiB	University of Bergen
VD	Vascular Dementia
WHO	World Health Organization

List of Publications

Paper 1:

Habiger TF, Flo E, Achterberg WP, Husebo BS: The Interactive Relationship between Pain, Psychosis, and Agitation in People with Dementia: Results from a Cluster-Randomised Clinical Trial. Behavioural Neurology 2016;2016:8.

Paper 2:

Habiger TF, Achterberg WP, Flo E, Husebo BS: Psychosis symptoms in nursing home residents with and without dementia-Cross-sectional analyses from the COSMOS study. Int J Geriatr Psychiatry 2019;34(5):683-691.

Paper 3:

Habiger TF, Achterberg WP, Flo-Groeneboom E, Mannseth J, Husebo BS. Managing Pain and Psychosis Symptoms in Nursing Home Patients: Results From a Cluster-Randomized Controlled Trial (COSMOS). J Am Med Dir Assoc. 2021;22(8):1692-8.

Other papers not included in the thesis:

Husebo, BS, Ballard, C, Aarsland, D, Selbaek G, Slettebo DD, Gulla C, Aasmul I, Habiger TF, Elvegaard T, Testad I, Flo E: The Effect of a Multicomponent Intervention on Quality of Life in Residents of Nursing Homes: A Randomized Controlled Trial (COSMOS). J Am Med Dir Assoc 2019;20(3):330-339.

Wagatsuma, S, Yamaguchi, T, Berge, LI, Husebo BS, Habiger TF, Nouchi, R, Angeles RC.: How, Why and Where it Hurts-Breaking Down Pain Syndrome Among Nursing Home Patients With Dementia: A Cross-Sectional Analysis of the COSMOS Trial. Pain Managr Nurse 2021.

Abstract

Background: In nursing homes (NH) >80% have dementia, and 30-60% experience pain daily. Psychosis symptoms (delusions and hallucinations) are common. These can lead to reduced quality of life (QoL) and are often treated with antipsychotic medication, which can cause harmful side-effects. Previous studies have suggested an association between pain and psychosis symptoms, but none have investigated the longitudinal association as well as the effect of pain treatment on psychosis.

Aim: To investigate the relationship between pain and psychosis symptoms, and the characteristics of NH patients with psychosis symptoms. The thesis also aims to investigate the effect of pain treatment on psychosis symptoms and the effect of a multicomponent intervention on psychosis symptoms and pain.

Methods: Paper 1 investigates the effect of pain treatment on psychosis symptoms and uses data from a cluster-randomized controlled trial (cRCT), the Pain-BPSD study. Papers 2 and 3 use data from a cRCT, the COSMOS-trial, and investigate the characteristics of NH residents with psychosis symptoms, as well as the association between pain and psychosis symptoms over time and the effect of a multicomponent intervention on pain and psychosis. Pain was measured using the MOBID-2 pain scale, while psychosis symptoms are measured using the NPI-NH.

Results: Paper 1 included 352 residents from 60 NH units, while the COSMOS-trial included 723 residents from 67 NH units. Pain treatment reduced psychosis symptoms ($p = 0.034$). Residents with psychosis had lower QoL ($p < 0.001$) and more depressive symptoms ($p < 0.001$). Pain was longitudinally associated with psychosis symptoms as a group ($p = 0.009$) and delusion individually ($p = 0.007$). The COSMOS-intervention had no effect on total pain or psychosis symptoms.

Conclusion: Pain in NH residents was associated with psychosis symptoms as a group and delusion individually. Psychosis symptoms were associated with depression and lower QoL. The effect of non-pharmacological interventions on psychosis symptoms needs further research.

Implications: Pain assessment should be a prerequisite when making treatment decisions on psychosis symptoms in NH residents. Thorough guidelines for treating psychosis symptoms in NHs need to be developed to reduce their negative impact.

Sammendrag

Bakgrunn: På sykehjem (SH) har over 80% demens, og 30-60% opplever daglig smerte. Psykosesymptomer er vanlig, kan føre til redusert livskvalitet, og behandles ofte med antipsykotika som kan gi skadelige bivirkninger. Tidligere studier indikerer en sammenheng mellom smerte og psykosesymptomer, men ingen har undersøkt den longitudinelle sammenhengen, eller effekten av smertebehandling på psykose.
Formål: Undersøke sammenhengen mellom smerte og psykosesymptomer, samt karakteristika til SH-pasienter med psykosesymptomer. Avhandlingen undersøker også effekten av smertebehandling på psykosesymptomer, samt effekten av en multikomponent-intervensjon på psykosesymptomer og smerte.
Metode: Artikkel 1 undersøker effekten av smertebehandling på psykosesymptomer, og analyser data fra den klynge-randomiserte kontrollerte, Pain-BPSD studien. Artikkel 2 og 3 bruker data fra den klyngerandomiserte kontrollerte KOSMOS-studien, og undersøker karakteristika til SH pasienter med psykosesymptomer, i tillegg til sammenhengen mellom smerte og psykose over tid, samt effekten av en multikomponent intervensjon på smerte og psykose. Smerte måles med MOBID-2 smerteskala. Nevropsykiatrisk intervjuguide – SH-versjon brukes for å måle psykose.
Resultat: Artikkel 1 inkluderte 352 pasienter fra 60 SH avdelinger, mens KOSMOS-studien inkluderte 545 pasienter fra 67 SH avdelinger. Smertebehandling reduserte psykosesymptomer ($p = 0.034$). Pasienter med psykosesymptomer hadde lavere livskvalitet ($p < 0.001$) og mer depresjonssymptomer ($p < 0.001$). Smerte var longitudinelt assosiert til psykosesymptomer som gruppe ($p = 0.009$), og vrangforestillinger individuelt ($p = 0.007$). KOSMOS-intervensjonen hadde ingen effekt på total smerte eller psykosesymptomer.
Konklusjon: Smerte er assosiert med psykosesymptomer som gruppe, og vrangforestillinger individuelt. Psykosesymptomer er assosiert med lavere livskvalitet, og har negativ påvirkning på SH pasienter. Effekten av ikke-farmakologiske intervensjoner på psykosesymptomer trenger videre undersøkelse.
Implikasjoner: Smertevurdering bør være standard når en skal vurdere behandlingsvalg for psykosesymptomer. Klare retningslinjer trengs for behandling av psykosesymptomer for å redusere de negative konsekvensene de har.

1. Introduction

My journey towards this dissertation and its topic has been long. It started in 2008 when I began to work at the local home-care service in my hometown, Haugesund. I visited many different older adults at home with different health challenges for which they received domiciliary care and was surprised at how many medications they used, thinking: “Wow, it must be hard to have so many diseases that you need to take so many medications. Do they really need all of them?”. Years passed by. I finished my bachelor’s degree in chemistry in 2011 and in 2012 started medical school, but every summer I returned to my hometown to work, first at the home care services, then at the nursing home (NH), and later at the hospital as a doctor. As my medical knowledge grew, so did my curiosity. How could I best help my patients, and how could I gain knowledge that would help me do this? The answer came to me when I was introduced to the Medical Students Research Program: “I have to discover new knowledge myself by doing research”, and after listening to my main-supervisor, Bettina Husebø, talking passionately about her new research project, the COSMOS-trial, which aimed to improve NH residents’ quality of life (QoL) through better Communication, Systematic pain assessment and treatment, Medication review, Organization of activities, and Safety, (1) I decided that I wanted to be a part of this.

When travelling around Norway during the COSMOS-trial, I observed how many NH residents were troubled by not only dementia but 2 or more additional diseases, also known as multimorbidity (2). This highlighted how complex and heterogenic the NH population is and how many aspects physicians and nurses must consider when deciding on treatments for their patients. Many experienced pain, and studies show that 30-60% of NH residents suffer from pain daily (3). I also observed that most patients used analgesics, although few were evaluated by a validated pain assessment tool before, and and after treatment. Due to the large number of patients using analgesics, I learned the ATC-code for both oxycodone (N02AA05) and paracetamol (N02BE01) by heart, after spending many hours plotting data from the COSMOS-trial into statistical software programs.

Another common feature in the NHs were behavioral disturbances, also called Neuropsychiatric symptoms (NPS). In fact, studies have shown that over 90% of people with dementia (PwD) suffer from at least one NPS during the course of their disease (4). These symptoms, among others, include agitation, depression, delusion, hallucinations, and sleep disturbances. There are many different NPS, but many of them have a common ground in that they are treated with psychotropic drugs, which can all cause potentially harmful side-effects (5, 6). This highlights the importance of finding any potential underlying factors to avoid the use of potentially harmful drugs. Surprisingly, when I searched the literature, to my surprise, it seemed that one of the symptom groups, psychosis symptoms, were not as thoroughly investigated as the others.

When I looked at all these different diseases and conditions, and that all of them were treated with different drugs, I thought it was no wonder that polypharmacy is a problem in a NH population (7). I then began to think of how my research could contribute to reducing this problem. Because psychosis symptoms were not extensively studied, it seemed to me that this was a good place to start, especially since the use of psychotropic drugs is very common in the treatment of these symptoms. Since pain was also very common, and research has previously found pain to be associated with other NPS such as agitation, (8) maybe this could also be a cause for psychosis symptoms? My first article found that pain treatment reduced psychosis symptoms, (9) this encouraged me to dig further into this subject, which made me realize that a single article was not enough to do this. I needed to perform multiple studies and achieve a PhD degree to answer my questions properly. The focus of this thesis is therefore to investigate NH residents with psychosis symptoms and to discover any potential underlying factors such as pain. It also investigates if a multicomponent intervention can reduce both pain and psychosis symptoms in NH patients. The first literature search for this thesis was performed in June 2014, and the last in June 2021, using relevant databases such as PubMed, EMBASE and GoogleScholar.

2. Background

2.1 Nursing homes and the nursing home population

In Norway there are approximately 700 NHs and 40 000 NH beds in total; 78% of the NH population are women, and 57% of all deaths occur in a NH (10, 11). Public health care services run 91% of the NH beds, while 5% are run by private non-profit organizations, and 4% by private commercial organizations (11). The mean length of stay in a NH is approximately 2-years, and the number of people aged 67 or older residing in a NH is 88% (11, 12).

The NH population is a diverse population where over 80% of the patients have dementia (13). NH patients often experience two or more diseases, as a study by Reilev et al. in 2019 has shown, where 47.5% of 5179 Danish NH patients had 2 or more comorbidities (14). This reflects the elderly population in general, as a study by Barnett et al. found that 64.9% of people aged 65-84 years experienced multimorbidity, while 81.5% of people ≥85 years did the same (2). Multimorbidity can complicate the treatment of NH patients, as different diseases and conditions require different treatment strategies that can interfere with each other, which again can lead to polypharmacy, a frequent challenge in NHs (5).

Polypharmacy is common in NHs, and recent studies have shown that NH patients receive on average 7-9 regular medications (5, 15, 16). The implications of polypharmacy have been demonstrated in different studies. In 2018 Vetrano et al. found that NH patients experiencing polypharmacy had a greater cognitive decline than their counterparts. Another study by Onder et al. in 2013 found that polypharmacy was associated with increased mortality in patients with advanced cognitive impairment (7, 17). Systematic medication reviews aimed at reducing polypharmacy can have a positive effect, as demonstrated by a recent meta-analysis by Kua et al. in 2018, who found that mortality and falls were significantly reduced in response to a medication review (18). A medication review can also improve elderly peoples QoL, as shown by Romskaug et al., who investigated the effect of a

collaboration between a geriatrician and a family physician on health related QoL in home-dwelling older adults with polypharmacy (19). This highlights the importance of prescribing, and deprescribing, the right drug to the right person at the right time.

The NH population is often frail, and patients live together in a closed environment. Therefore, NHs are often more vulnerable to outbreaks of infectious diseases than the community in general, something highlighted during the COVID-19 pandemic, where, globally, 19 – 72% of all COVID-19 related deaths occurred in a NH (20). A Dutch study by Rutten et al. found that in NH patients with confirmed COVID-19 the mortality risk increased threefold (21). The vulnerability of the NH population also led to NH patients receiving high priority for COVID-19 vaccination in Norway. However, as the mRNA-vaccine provided to the NH residents has potential side effects, it was important to investigate whether side-effects from the vaccine could increase mortality in NH resident. A study by Wyller et al. investigated if the vaccine led to a fatal adverse reaction in 100 suspected cases in Norwegian NHs. They reviewed 100 suspected cases of a fatal adverse reaction and found a probable causal link to vaccination in 10 of them (22). As the general mortality rate in NHs is high, this was not a high number; nevertheless, the findings highlight the importance of a risk-benefit assessment when deciding whether to vaccinate a NH resident.

By law, all Norwegian citizens have a guaranteed right to necessary health- and care services provided by their municipality, which, if needed, includes care in a NH (23). The law also states that all patients and users of the health care system have the right to care with dignity (23, 24). Each NH patient therefore has the right to take part in the decision-making process concerning their own treatment, and the use of compulsory treatment is limited to situations where it is absolutely necessary (23, 25) (Appendix 1). This provides the legal framework on which physicians, nurses and other care workers must base their treatment decisions, and these are important to keep in mind when dealing with the complex situations that can arise in a NH, where the use of compulsory treatment is considered an option.

2.2 Dementia

Dementia is an increasing global challenge affecting approximately 50 million people worldwide, a number that is expected to rise to 82 million by 2030, and 140 million by 2050 (26). The largest increase is expected in low- and middle-income countries. Dementia is a group of neurodegenerative diseases that are characterized by progressive cognitive decline. As the disease progresses, people become increasingly functionally dependent. Depending on how the cognitive impairment affects the PwD, dementia can be broadly divided into three clinical stages (27): Mild, where the cognitive impairment affects the ability to perform day to day activities; moderate, where the PwD is unable to function without the help of others; and severe, where the PwD needs continuous care.

2.2.1 Types of Dementia diseases

The most common type of dementia is Alzheimer's disease (AD), but other types of dementia such as vascular dementia (VD), Lewy-Body dementias (LBD), and frontotemporal dementia are common. Dementia can also be caused by acquired brain damage, due to, for example, trauma or substance abuse. (27)

Alzheimer's Dementia

The most common form of dementia is AD, which accounts for 60-80% of PwD (28). The pathophysiology of AD is not fully understood suggested mechanisms include the accumulation of β-amyloid protein-plaques as well as the accumulation of an abnormal form of the tau-protein, which forms tangles within neurons. This accumulation interferes with normal neuron-to-neuron signaling, as well as the transport of nutrient to the cells, which can lead to cell-death and atrophy (28, 29). It is also thought that chronic inflammation plays an important role due to the increased number of plaques and tangles and the inability of microglia to remove the toxic proteins as well as the increasing amount of cell-debris (28, 29).

Vascular dementia

Vascular dementia (VD), is, broadly speaking, is dementia due to cerebrovascular disease, is thought to be the second most common type of dementia, responsible for 15-20% of dementia cases (30). There are different subtypes of VD according to the cause and site of the cerebrovascular disease, which, among others, include multi-infarct dementia, small-vessel dementia and hypoperfusion dementia (30). A stroke is a common cause of VD, but not all patients who have a stroke develop dementia; studies show that 20-25% of patients with a stroke develop dementia (30). As both AD and VD share many common risk-factors, the co-occurrence of the two, especially in late stages of dementia, are common, and autopsy studies have suggested that mixed dementia may be the most common dementia cause in late-life and thus in the NH (30-32).

Lewy Body dementia (LBD)

Lewy-Body dementia, includes both dementia with Lewy-Bodies (DLB) and Parkinson's disease dementia (PDD) (33, 34). Both dementias share many similar clinical and neuropathological features, especially the aggregation of inclusion bodies with α-synuclein called Lewy-Bodies (35). Despite their similarities, the two dementia-types are often distinguished on the basis of the onset of motor symptoms (parkinsonism) in Parkinson disease (PD) (34). In PDD, dementia occurs at least 1-year after the onset of the motor-symptoms of PD, while in DLB, dementia occurs before, or concurrently with, parkinsonism (34). DLB are characterized by its fluctuating course, which can often resemble delirium with a change in cognitive function and alertness occurring within a relatively short period of time (34, 36). Another feature often found in DLB are hallucinations, which can occur in up to 80% of patients, often in the form of visual illusions and a sense of presence (34, 37).

2.2.2 Treatment of dementia

Effective curative treatment options does not exist for either AD or LBD, leading to the development of symptom relieving drugs, mainly targeting neurotransmission (38, 39). The medications currently approved for treatment of AD, and also LBD, can

mainly be divided into two groups: acetylcholinesterase-inhibitors (ACI) and N-methyl-d-aspartate (NMDA) receptor inhibitors (38-41). In the ACI group, rivastigmine, donepezil and galantamine are approved, while memantine is a recommended NMDA-inhibitor (38). In AD, the use of ACI usually provides the largest benefit in people with mild to moderate dementia, while the use of memantine is indicated in moderate to severe dementia (38, 41). In LBD the effect and side-effects of rivastigmine and donepezil are thoroughly documented. While there is a need for more trials regarding the effect of memantine, studies have shown that patients with LBD can benefit from using the drug (39, 42, 43). However, it is crucial to recognize that the anti-dementia drugs' effect relies on slowing the disease progression in some PwD, but they are not able to halt the disease.

The lack of curative treatment highlights the need for supportive measures to ensure a good psychosocial environment for PwD and their family and help them manage their disease. This includes home-care services, adult day-care centers, and as the disease progresses, care in a Nursing Home (NH) (44). The Norwegian directorate of health has developed thorough guidelines for the management of PwD in different stages of the disease, where the importance of psychosocial measures are highlighted (31).

2.3 Neuropsychiatric symptoms

Behavioral and Psychological symptoms of Dementia (BPSD) are common features seen in NH patients with dementia. Such behavioral changes include both affective and psychological symptoms. However, these symptoms also affect people without dementia, and when referring to these symptoms in a general population, not only in PwD, they are named neuropsychiatric symptoms (NPS) (32). Twelve of the most common symptoms included in the Neuropsychiatric Inventory – Nursing home version (NPI-NH) are as follows: delusion, hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, aberrant motor behavior (AMB), disinhibition, sleep disturbances, and appetite disturbances (4). NPS are common in NH patients, and especially in PwD where over 90% of patients suffer from at least one NPS during the course of their disease (4). Some of the symptoms often coexist or concur,

which has led to a variety of studies investigating which symptoms most often occur together, and if they do so over time, thereby making up a symptom cluster. A selection of these studies is found in Table 1. Most studies show that some symptoms are consistently related to one of the following three clusters: depression and anxiety in a mood/affective cluster, agitation and irritability in an agitation cluster, and delusion and hallucination in a psychosis cluster. Furthermore, during the course of the disease, PwD may develop different NPS with across these clusters (45).

Table 1: Symptom clustering of NPS

Authors	Year	Symptom clusters
Hollingworth et al. (46)	2006	*Behavioral dyscontrol:* Euphoria, Disinhibition, AMB[a], Sleep Disturbances and Appetite Disturbances *Psychosis:* Delusion and Hallucinations *Mood:* Depression, Anxiety and Apathy *Agitation:* Aggression and Irritability
Aalten et al. (47)	2008	*Hyperactivity:* Agitation, Euphoria, Disinhibition, Irritability and AMB *Psychosis:* Delusion, Hallucinations and Sleep Disturbances *Affective:* Depression and Anxiety *Apathy:* Apathy and Appetite Disturbances
Selbaek et al. (45)b	2012	*Psychosis:* Delusion and Hallucinations (Euphoria) *Affective:* Depression and Anxiety *Agitation:* Agitation, Disinhibition and Irritability (AMB) *Apathy:* Apathy, (Appetite Disturbances) *Sleep disturbances not consistently in one cluster*
Cheng et al. (48)	2012	*Behavioral problems:* Agitation, Disinhibition, Irritability and AMB *Psychosis:* Delusion and Hallucinations *Mood disturbances:* Depression, Anxiety, Apathy, Appetite Disturbances and Sleep Disturbances *Euphoria not consistently in one cluster*

a: Aberrant Motor Behavior

b: Patients who were followed the entire study-period of 31 months

2.3.1 Psychosis symptoms

The core symptoms of psychosis is the loss of a person's ability to distinguish between what is real from what is not due to the disruption of their thoughts or

perception, often expressed through hallucinations or delusions (49). Delusion in PwD is usually not as complex as in patients with schizophrenia, and often include beliefs of theft or paranoid delusions of being cheated on by a partner. (50) A specific type of delusion is misidentification, often viewed as a separate psychosis symptom, where family or caregivers are thought to be imposters, or their home is not though to be their home (50). Hallucinations are usually of the visual kind, but auditory hallucinations can occur, especially in people with hearing impairment. Visual hallucinations also occur in people with visual impairment, without neurological disease, a phenomenon referred to as Charles Bonnet's syndrome (51). Psychosis symptoms are more common in patients with DLB and PDD than in patients with AD (32, 34, 37, 50). In AD, psychosis symptoms most commonly debut as the disease progresses from moderate and severe dementia, and they can be present even earlier in patients with PDD and DLB (50, 52). In VD, the presentation and timing of psychosis symptoms depends on the extent and location of cerebrovascular injury, but it does not share a pattern similar to that of AD (50, 53, 54).

Symptoms of psychosis such as hallucinations and delusion are often found within a NH population. The prevalence varies according to different studies, as the use of assessment tools and methods differ. In general, the prevalence of delusion varies between 13 % to 25%, while the prevalence of hallucinations varies between 5% to 18% (4, 55-58). It seems that psychosis symptoms are one of the more stable NPS through the course of a dementia disease. However, studies have indicated that they are more prevalent in moderate to severe dementia, compared to mild dementia, particularly in people with AD (4, 59, 60).

Causes and consequences of psychosis symptoms

The most common cause of psychosis symptoms in NH patients is dementia, but there are various other factors that can trigger or cause psychosis symptoms (52, 61). Second to dementia, one of the major causes of psychosis symptoms in NH patients is delirium (61, 62). Delirium is characterized by acute changes in cognition and awareness, often followed by agitation, hallucinations, and delusion, and can be

thought of as “acute brain-failure” (62). Delirium can occur in all people, including PwD, and may be triggered by several different factors such as infection, surgery, and medications (62, 63). Psychosis symptoms caused by delirium have some similarities with psychosis symptoms deriving from NPS, but perhaps the main difference lies in their acute nature (62, 64). An overview of similarities and differences is found in table 2 (50, 52, 62-64).

Different medical conditions can also cause psychosis symptoms in older adults, e.g., severe electrolyte disturbances such as hyponatremia and hypercalcemia, hypo- and hyperglycemia, uremic encephalopathy, and hepatic encephalopathy (61, 65). Various medications have the potential to cause psychosis symptoms, often through anticholinergic side-effects, but other medications such as corticosteroids are also known to cause psychosis symptoms (66, 67). Environmental factors such as lack of company and meaningful activities have also been found to be associated with psychosis symptoms (68).

Psychosis symptoms in NH patients can have a negative impact on both patients and caregivers and may be associated with a more rapid cognitive decline and increased mortality risk (52, 69) Both Wetzels et al. in 2010 and Mjorud et al. 2014 found that psychosis symptoms were associated with poor QoL in PwD residing in NHs (70, 71). In 2016, Helvik et al. investigated the severity of NPS in NH residents and found that the severity of psychosis symptoms was associated with poor physical health and the use of psychotropic drugs such as antipsychotics and anxiolytics (72), although the impact on QoL seems to be related to the type and nature of each symptom. For instance, Cohen-Mansfield et al (2016) investigated the impact of psychosis symptoms on patients experiencing them and found that half of people with delusions experienced discomfort, whereas 36% of patients with hallucinations reported the same (73).

Table 2: Psychosis symptoms as a NPS compared to psychosis symptoms as a part of delirium		
	Neuropsychiatric symptoms (NPS)	Delirium
Onset	Gradually – NPS develops for weeks/months	Acute – usually, delirium develops for hours/days Characterized by an acute change of normal behavior.
Individuals	Affects people with diseases/conditions by affecting the central nervous system	Can affect all people. Frail people and PwD are more at risk.
Attention	Generally normal	Disturbed attention and awareness
Psychosis symptoms	Can include hallucination, delusion, and misidentification. Visual hallucinations more common than auditory.	Both delusion and hallucination can occur. Usually accompanied by agitation in hyperactive delirium.
Course	AD: Usually stable, some fluctuation can occur PD and DLB: Usually a fluctuating course	Fluctuating during the day
Duration	Months/Years	Hours/Days/Weeks – depends on the underlying cause
Cause/Contributing factors	Unmet needs (e.g., lack of sleep, boredom, loneliness, feeling of isolation), polypharmacy, pharmacological side-effects, sensory deficits (hearing or vision-impairment).	Infection, surgery, pharmacological side-effects, myocardial ischemia, **pain**, environmental changes. All diseases and injuries have the potential to cause delirium.
Assessment	NPI-NH, BEHAVE-AD	Confusion assessment method (CAM), 4AT
Treatment	Non-pharmacological – first option - Treat potential underlying factors - Person centered care Pharmacological treatment: - Only in cases where the patient is at risk of harm, or of harming other patients - Short duration of time – up to 6 weeks before reduction/withdrawal should be attempted - Risperidone the preferred medication - In patients with PD or DLB, use of clozapine can be considered in specialized care	<u>Find and treat the underlying cause.</u> Non-pharmacological measures first option: - Single-room, shield the patient from disturbing stimuli, orientation for reality. - Promote sleep Pharmacological treatment: - In cases of severe aggression where the patient is in risk of harm: Antipsychotic medication, such as haloperidol. Clomethiazole to promote sleep in some cases. Diazepam an alternative to antipsychotics.

2.3.2 Other neuropsychiatric symptoms

The prevalence of each NPS varies between studies, depending on the applied assessment tools and different method measurements in various studies. A study by Roen et al. in 2017 investigated the characteristics of 696 Norwegian NH patients at admission and found that the most prevalent symptoms were depression (21.5%) followed by anxiety (20.4%) and irritability (17.8%) (56). A prospective cohort study by Selbaek et al. in 2014 investigated the course of 12 different NPS in 931 NH patients with dementia for 53 months (4). At baseline, irritability (29.2%), apathy (28.8%) and agitation (26.5%) were the most prevalent symptoms. The cumulative prevalence after 53 months demonstrated that 64% of patients experienced irritability at least once during the 53-month period, while 60% experienced apathy and 52% agitation. Results are supported by Wetzels et al (2010) who investigated 173 Dutch NH patients with dementia. Over the course of two years, they found irritability (28.2%), AMB (23.1%) and agitation (20.5%) to be the most prevalent. After two years the cumulative prevalence showed that irritability (58.1%) was still most common followed by agitation (53.8%) and apathy (53.0%) (59).

Causes and consequences of other neuropsychiatric symptoms

It is important to identify potential triggers and underlying causes of NPS, as this can aid the use of non-pharmacological treatments directed at a specific cause to eliminate them and thereby avoid the use of pharmacological treatment, which can cause harmful side-effects for patients (6).

The main cause of NPS is neurodegenerative disease such as AD, and symptoms have been shown to increase in frequency with dementia severity (13). However, the etiology of NPS remains multifactorial, impacted by different environmental, psychological, and physical factors such as hearing and vision (74, 75). A study by Steinberg et al. from 2006 investigated different risk factors for NPS in PwD and found that a high degree of comorbidity was associated with the prevalence of agitation symptoms such as aggression, disinhibition and AMB (76). The association between comorbidity and NPS is further highlighted in a study by Hodgson et al. who

in 2011 found that 36 % of PwD who experienced NPS had an undetected illness such as an infection, anemia or diabetes mellitus (77). A recent study by Michelet et al (2021) found that affective NPS could be triggered by unmet needs such as a lack of daytime activities and loneliness (68). As is discussed in detail in this thesis, the association between pain and NPS has also drawn attention, and different studies have found that pain could be a potential trigger for both affective NPS, psychosis symptoms and agitation (78-80).

NPS symptoms can influence individuals in different ways, and have consequences for the person who is affected, their families, and caregivers alike. (81) Some of the symptoms such as agitation and depression can be stressful for the family, as shown in a review by Cheng et al. in 2017, who found that NPS, and especially agitation, increased caregiver burden and could lead to depression in caregivers (82). The association between NPS and institutionalization is highlighted in a study by Okura et al (2011), which showed that both agitation and depression increased the risk for the institutionalization of patients (83). NPS also has a negative impact on caregivers in NHs, as found by Zwijsen et al (2014), where aggression and disinhibition caused the most staff distress, while apathy and euphoria caused the least (84). The negative impact of NPS on NH patients' QoL has been shown in previous studies. Wetzels et al. investigated determinants for QoL in NH patients with dementia and found that agitation and depression reduced the QoL (71). Results were supported by Mjorud et al (2014), who demonstrated the association between agitation and affective NPS, with poor QoL (70).

2.4 Treatment of neuropsychiatric symptoms

2.4.1 Treatment of psychosis symptoms

Non-pharmacological treatment

Evidence-based guidelines on the treatment of NPS and psychosis symptoms in NH patients with dementia have stated that the first-line treatment should be to assess and treat potential underlying causes, before using pharmacological options (31, 85). The evidence of the effect of non-pharmacological measures on NPS such as agitation and

depression has been well-documented in randomized controlled trials (RCT); however, evidence of the effect of a specific treatment, directed at psychosis symptoms in NH patients, is lacking (50, 52, 85, 86). In general, the most successful non-pharmacological interventions are personalized, individually tailored to the symptom and to the patient. This highlights that there is no one-size-fits-all treatment for any of the NPS and psychosis symptoms in particular (86-88).

A promising method in the treatment of NPS is the Describe-Investigate-Create-Evaluate (DICE) approach, developed and tested by Kales et al (2014), which is based on four phases 1) Describe-phase: NPS are characterized by what type of NPS is being presented and at which time and situation they occur. 2) Investigate-phase: Caregivers investigate possible causes for NPS, such as untreated illness or functional limitations. 3) Create-phase: A plan for treatment of the NPS based on the previous investigations is made. 4) Evaluate-phase: The effectiveness of the treatment-plan is assessed. (74)

Studies using a similar framework have shown the most promising results on NPS (89-93). However, few of them focus on the specific effect on psychosis symptoms. One of the few studies where the effect of a multicomponent non-pharmacological intervention on psychosis symptoms is measured is the Targeted Interdisciplinary Model for Evaluation and treatment of NPS (TIME), developed by Lichtwarck et al (2018) (89). TIME is based on person centered care and cognitive behavioral therapy, and consists of thorough assessments of NPS, development of a treatment plan followed by an evaluation of the treatment (94). The efficacy of the TIME-intervention was investigated in a RCT including 229 Norwegian NH patients with dementia, and this showed a small positive effect on delusion but not hallucinations or psychosis symptoms as a group (89). Another promising approach is the Grip on Challenging behavior developed by Zwijsen et al., which uses a multidisciplinary stepwise care program to treat NPS (93). The effect of this approach on psychosis symptoms has been studied and showed a significantly positive effect on delusion in 659 NH residents with dementia (93).

Pharmacological treatment

If no treatable underlying causes have been identified, and non-pharmacological options have been attempted, the use of the atypical antipsychotic risperidone has been recommended as the best available option (52, 85, 95). According to Norwegian guidelines (2017), the next pharmacological choices are off-label use of the atypical antipsychotics aripiprazole or olanzapine (31). However, in people with PDD and DLB, the use of antipsychotics with high dopaminergic activity may cause serious side-effects. Thus the prescription of the low dose atypical antipsychotic clozapine is recommended. To oversee safety issues and the risk of agranulocytosis, the treatment should be limited to specialized-care units (31, 96). In PDD, there is emerging evidence that the selective serotonin 5-HT inverse agonist, pimavanserin, could have a positive effect (96, 97). However, for psychosis symptoms in PDD patients, the reduction of PD-medication dosage while maintaining the clinical effect on PD can be enough to manage psychosis symptoms (96).

The use of pharmacological treatment is often preferred by physicians. A study by Rashid et al (2021) investigated medication treatment patterns for dementia-related psychosis in 11,921 US NH patients and found that 77.3% of the patients received one or more antipsychotic drugs (98). A related review by Randle et al (2019) investigated the mortality for intermittent antipsychotic drug prescription in older-adults and found that conventional antipsychotics (e.g., haloperidol) increased the mortality, while the evidence for atypical antipsychotics was less clear (99).

Deprescribing studies

In 2009, Ballard et al. investigated the effect of the withdrawal of antipsychotic medication in 165 NH patients with dementia through a randomized placebo-controlled trial (DART-AD trial) and found that, compared to placebo, antipsychotics increased the mortality rate significantly (6). Also, other studies have investigated the effect of deprescribing antipsychotic medication. Brodaty et al (2018) investigated the effect of an educational program on NPS management and prevention, combined with a deprescribing protocol for antipsychotic medication, and found that the

number of patients using antipsychotics was reduced by 81.7% with no increase in NPS or adverse outcomes (100). When deprescribing antipsychotic medications, it should also be accompanied by nonpharmacological measures. The importance of such research was highlighted by Ballard et al (2016) in a cluster-randomized controlled trial where they investigated the effect of antipsychotic review with and without a social intervention, which included training in person-centered care (101). The study found that patients receiving antipsychotic review without an additional social intervention experienced an increase in NPS (101). This highlights the complexity in treatment of both psychosis symptoms and NPS in general, and why a thorough assessment of symptoms and possible underlying causes is important before making treatment decisions.

2.4.2 Treatment of other neuropsychiatric symptoms

Non-pharmacological treatment

Comparable to treatment recommendations for psychosis symptoms, the guidelines for the management of other NPS (e.g., agitation and depression) highlight that the first option is the use of non-pharmacological measures (102). The value of specific non-pharmacological measures has been shown, although the methodological quality, control conditions, sample sizes, and valid outcome measure of studies differ significantly (88). A systematic review by Abraha et al (2017) found music-therapy and caregiver-oriented interventions (e.g., personalized activities) most promising and especially effective in cases of anxiety and agitation (87). The DICE-approach, mentioned above, is a valid basis for how to develop treatment plans for NPS, and different similar interventions have been tested for efficacy (74). The most promising results have come from studies using a stepwise approach where measures are tailored to each individual person (89-93).

One of these is the Staff-Training in Assisted-living Residences (STAR-VA) program consisting of a psychosocial intervention targeting behavioral disturbances such as agitation and depression (90). A study published by Jedele at al (2020), including 302 veterans residing at community living centers, investigated the effect of the STAR-

VA program on NPS and found that the program had a positive effect on agitation, depression, and anxiety (90). The TIME-intervention, previously described, has been found to have a significant positive effect on agitation (89). A multicomponent intervention-study focusing on staff-training (STA-OP) by Pieper et al (2016) has also been shown to reduce depression and challenging behavior in NH patients with dementia (91). In 2017, Gitlin et al. developed a tailored activity program (TAP) in collaboration with an occupational therapist and tested its efficacy on behavioral disturbances through a single-blind RCT trial (TAP-VA), including 160 home-dwelling PwD and their caregivers (92). The TAP-VA intervention was effective in reducing the number of behavioral disturbances, as well as their frequency and severity (92). It is difficult to recommend one specific type of non-pharmacological intervention, but the most promising results comes from the interventions where the measures taken are tailored to each person.

Pharmacological Treatment

Norwegian guidelines and international recommendations state that if treatment with non-pharmacological options is unsuccessful, then the use of pharmacological treatment with psychotropic medication is recommended for a short duration of time, and no longer than 12 weeks before discontinuation should be attempted (31, 74). However, guidelines also state that the use of such drugs is only warranted in cases of severe agitation, or when the NPS puts the patients or persons around them at serious risk for harm. Norwegian guidelines recommend pharmacological options for agitation similar to those for psychosis symptoms, with the use of the antipsychotic risperidone recommended as a first-choice and off-label use of aripiprazole or olanzapine as a second-choice (31). Despite guidelines stating that non-pharmacologic treatments are the first option, the use of psychotropic drugs is high. A study by Gulla et al (2016) investigated the use of psychotropic drugs in 129 Norwegian NHs and found that 41% of patients used two or more psychotropic drugs (103). A similar trend was found by Helvik et al. in 2017 who in a 72-month longitudinal study, investigated the use of psychotropic drugs in 1,163 NH residents (104). They found that over 32% of patients used antidepressants at any point in time,

while over 20% used antipsychotics and over 22% used anxiolytics (104). A similar trend can be seen in other European countries, although the prevalence varies between countries, as found by Janus et al. who in 2016 performed a literature review of the use of psychotropic drug use in western European NHs (105). They found that the use of antipsychotic drugs varied between 12-59%, while the use of antidepressants varied from 19-68% (105).

Consequences of psychotropic drug use

The high use of psychotropic drugs has several downsides due to the risk of side-effects. Aspinall et al. (2019) investigated the risk of recurring falls in older adults aged ≥65 years using CNS-acting drugs, including antidepressants, anxiolytics, and antipsychotics, and found that an increased use of CNS-acting drugs was associated with risk of recurring falls (106). Results are supported by Bakken et al (2016), who investigated the association between the use of antipsychotics and hip-fractures in people aged ≥60 years and found that use of first- and second-generation antipsychotics were associated with a higher risk of hip-fractures (107). The risk of severe side-effects is also highlighted by a systematic review by Wang et al. (2015), which demonstrated that the use of atypical antipsychotics increased the risk of adverse events (108). A recent cross-sectional study by Ito et al. on 431 Norwegian NH patients have also suggested that the use of psychotropic drugs is associated with lower QoL (109).

In 2013, Ruths et al. published a study investigating the use of psychotropic drugs in Norwegian NHs from 1997 to 2009 and found that the prevalence of all psychotropic drugs increased from 57.6% to 70.5% (110). In contrast to this, an encouraging trend in the use of antipsychotic medication in Norway has been seen, as shown by Selbaek et al. in 2017, who found that the use of antipsychotic drugs in Norwegian NHs significantly decreased from 2004 to 2011 (111). Despite this, there is still a need to reduce the use of psychotropic drugs to the patients who benefit from the treatment and identify treatable underlying causes of NPS.

2.5 Pain in older adults

The definition of pain stated by the International Association for the Study of Pain (IASP) is: “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.” (112). The definition was expanded on by the addition of six different key notes, which highlights that pain is always a personal experience and influenced by biological, psychological and social factors. IASP also states that that pain and nociception are different phenomena; a person, through individual experiences, learns what pain is; and a person’s experience of pain should always be respected. Finally, they state that pain, despite its adaptive role, may have adverse effects on function, and social and psychological well-being, and that a verbal description is only one of several ways to express pain, meaning that inability to communicate does not negate the possibility that a person experience pain. This definition has helped researchers on pain in dementia that pain can be expressed in nonverbal ways.

Pain processing in older adults

The pain processing system consists of two parts (113, 114). The lateral pain system involves peripheral nociceptors that transmit their signals through the dorsal horn and spinothalamic tract to the lateral thalamus and somatosensory cortex. The latter is also named the sensory discriminative system and mainly controls the recognition of pain localization, the intensity and nature of the painful stimuli (113, 114). In addition, the medial pain system involves the amygdala, hippocampus and hypothalamus. This system is more complex and regulates the cognitive-evaluative aspects (assesses the cause of pain), memory, and the autonomic response to pain (113, 114). As people get older, their perception of pain can change. A meta-analysis by Lautenbacher et al. (2017) showed that the pain threshold, meaning the point where an individual starts to experience pain, increased in older adults (115). Pain tolerance, meaning the point where the pain becomes unbearable, remains unchanged, although there is a tendency towards reduced rather than increased tolerance (115, 116).

Pain in people with dementia

Dementia is an important aspect that can affect pain in older adults. A study by Kunz et al. (2009) investigated the impact of dementia on different components of pain and found that people with a reduced ability to self-report had a reduced autonomic response to pain (117). They also found that PwD showed increased facial responses to acute pain compared to their healthy counterparts (117). However, as the painful stimuli used in the study can be defined as acute pain, it is difficult to say if the results are transferable to chronic pain, which is most common in NH patients with dementia. This is important to note when performing a pain assessment of PwD, as acute pain can be detected more easily than chronic pain, which needs a longer time of observation to detect.

The loss of self-report ability combined with the findings that PwD do not experience less pain than their cognitively healthy counterparts puts them at risk for undertreatment of pain (118). In AD, it seems that neuropathological changes affect the medial pain system, and thereby the motivational-affective aspects of pain to a larger degree than the sensory-discriminative aspects of pain (113). This means that pain theoretically may be more confusing and difficult to process producing more overt pain behavior (113, 119). The role of dementia severity was studied in a cross-sectional study by van Kooten et al. (2017) who investigated the association between dementia severity and the prevalence of pain in 199 Dutch NH patients (120). They found that patients with severe dementia had a higher prevalence of pain compared to patients with less cognitive impairment (120). Despite numerous studies on how dementia affects pain-perception and processing, crucial uncertainties still exist as reviews by Achterberg et al. (2013) and Borsook et al. (2012) have shown (121, 122). The impact of various neuropathological changes in dementia on pain processing is especially ambiguous, and some discrepancy between experimental and clinical findings are found (121, 122). There is, however, strong evidence for the loss of ability to self-report pain as dementia disease progresses, which is important to keep in mind when assessing pain in PwD (123).

Prevalence, consequences and causes of pain in nursing home patients

Pain can impact older adults negatively and have been found to significantly reduce the QoL and increase negative affect in NH patients. (124, 125) The prevalence of pain in NH patients varies greatly according to country and measurement tools used. A study by Achterberg et al. (2010) investigated the prevalence of pain in 10015 NH residents from three different European countries. Utilizing data from the minimum data set (MDS), the prevalence of any type of pain was found to be 57% in Finland, 43% in the Netherlands, and 32% in Italy (3). A Swedish study by Hemmingsson et al. investigated the prevalence of pain in 2007 and 2013 in 4933 NH residents. Using a dichotomous questionnaire (pain/no pain) they found that pain prevalence remained relatively stable at little over 60% (126). A systematic review by Takai et al. (2010) investigated the prevalence of pain in NHs and found large variations between 4% and 80% depending on which method was used to measure pain (127).

Pain location in people with dementia

Pain related to musculoskeletal pain such as back pain, pain from arthritis in the hip and knee, or pain due to old fractures are the most common causes of pain (128-130). A systematic review of the literature by Abdulla et al. in 2013 described studies on the location of pain in older adults, and highlighted back pain, pain from the legs, hips and knee joint as most common (131). Women were also found to experience pain more often than men (131). Results are supported by Wagatsuma et al. (2021), who found that the most common pain location was the legs and hip, followed by back and pelvis (132). However, neuropathic pain, caused by injury or disease in the peripheral or central nervous system (e.g., polyneuropathy in diabetes mellitus or stroke) may be hard to assess and treat (133). This is especially true in people with VD, as they can experience central neuropathic pain due to white matter lesions which disrupt the normal pain-processing pathways (134).

2.5.1 Pain assessment

As pain is a subjective feature, where the same painful stimuli can affect people in different ways, the gold standard of all pain assessment is self-report (135). For

people without cognitive impairment, or mild dementia, there are three assessment tools which can be recommended: The Visual Analogue Scale (VAS), the Numerical Rating Scale (NRS) and the Verbal Rating Scale (VRS) (136). All assess pain through self-report from no pain to either severe or worst possible pain, where the NRS uses numbers 0-10, VAS uses a continuous line from no pain to worst possible pain, and VRS uses 4 different categories, rating pain as none, mild, moderate or severe (136). However, in people with moderate or severe dementia, the use of these tools is not straightforward, and results are less valid (130, 135, 137).

As the dementia disease progress, skills such as memory, and communicative ability, can be impaired, which poses a challenge in assessment of pain (138). The ability to remember previous pain-experiences, and to compare present pain with previous pain, is especially important when treating pain, as this is a prerequisite in order to assess treatment effect (138). Memory is also an important factor to aide in identifying the cause of pain since this can aide physicians in making correct treatment decisions. If the patient cannot remember when and in what situation the pain occurred, then diagnosis of the cause of pain becomes complicated.

When individuals with dementia are no longer able to assess their pain, a proxy-rater is needed; this is a person who interacts with and knows the person well and can help assess the patients' pain (123, 137). Proxy-raters are encouraged to observe typical behaviors of pain, such as facial expressions, vocalization/noises, body language/defense, and changes in activity (130, 137). During the last 35 years, more than 40 pain assessment instruments have been developed to assess pain in people with cognitive impairment. However, some of these tools are used more often than others, and four of the most common are described in table 3 (139). Several systematic reviews of the literature described the development and psychometric property measurements of different instruments. However, there is no final consensus on which an instrument should be officially recommended (139). In our studies, we utilized the Mobilization-Observation-Intensity-Behavior-Dementia Pain Scale (MOBID-2), which is thoroughly tested for both validity, reliability, and

responsiveness (140-142). These are psychometric properties which are needed in order to detect change in pain over time, and response to pain treatment in PwD accurately.

Despite the fact that many pain tools are available, pain can often go unrecognized in PwD, especially since pain may trigger atypical behavior such as agitation, depression or sleep disturbances, also described as NPS (116, 137). In order to detect pain in PwD, pain assessment must be done routinely, which is not always the case, as shown in a study by Nakashima et al. (2019) (143). In a cross-sectional study including 50,673 NH residents, they investigated different pain interventions applied to PwD and cognitive healthy counterparts, and less pain assessments was done in PwD (143). A systematic review of the literature on qualitative studies by Knopp-Sihota (2019) demonstrated that lack of knowledge, cognitive impairment, and communication were the most prominent barriers in healthcare professionals (144). The main facilitators were found to be knowledge regarding pain-related behaviors, experience and skill in health-care professionals, and the presence of guidelines and protocols for pain assessments (144).

Table 3: A selection of some of the most used pain assessment tools for PwD

Assessment tool	Published by	Assessments	Rating
Mobilization-Behavior-Intensity-Dementia pain scale part 2: (MOBID-2)	Husebo et al. (140, 141)	Observe pain behavior (10 items): - Vocal - Facial expressions - Defense reactions During: - 5 Active guided movements - Last week in normal day to day activity for signs of pain in internal organs, head and skin	Staff members who know the patient well rate pain for each item and total pain on a NRS 0-10, where 0 represents no pain, and 10 worst pain possible
Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC)	Fuchs-Lacelle et al. (145, 146)	Observe pain behavior (60 items): - Facial Expressions - Activity/Body movements - Changes in social interaction/mood/personality - Physiological Changes - Changes in appetite/sleep - Vocal Behaviors During: Normal day to day activity	Staff members who know the patient well rate each behavior as present or not
Pain Assessment in Impaired Cognition (PAIC15) - Meta-tool	Kunz et al. (147)	Observe pain behavior (15 items): - Facial Expression - Body Movements - Vocalization During: - Rest - Activities of Daily living (ADL) - Activity - Observe for at least 3 minutes before assessment	Staff members who know the patient well rate each behavior on a scale from 0 to 3, where 0 represents "not at all" and 3 represents "to a great degree".
Pain Assessment in Advanced Dementia scale (PAINAD)	Warden et al. (148)	Observe pain behavior (5 items): - Breathing, independent of vocalization - Negative Vocalization - Facial Expression - Body Language - Consolability During: - Observation for at least 5 minutes - Patients observed under rest and activity	Staff members who know the patient well rate each item on a scale from 0 to 2, where 0 represents "normal" and 2 represents "severely disturbed"

2.6 Pain Treatment in older adults

In 2009, the American Geriatric Society (AGS) published their guideline for pharmacological management of persistent pain in older adults (149). However, in light of the current increased use of opioid analgesics, recent reviews and guidelines have recommended increased focus on non-pharmacological options for the treatment of pain in addition to pharmacological options (116, 150).

Non-Pharmacological treatment of pain

A variety of non-pharmacological options exists as an alternative in pain treatment; however, the effect on older adults and NH patients can be uncertain (131). The reason for this is that studies investigating the effect of non-pharmacological treatments often exclude elderly people, as well as frail people such as PwD and NH patients (131). A meta-analysis by Lee et al. (2016) systematically reviewed the literature on RCTs investigating the efficacy of music-therapy on pain, and found an overall positive effect on pain (151). However, the review did not investigate studies in older adults specifically. Non-pharmacological treatments that have been shown to have an effect on pain in older adults include massage, exercise, transcutaneous electric nerve-stimulation (TENS), and cognitive therapy (131, 150, 152). However, the quality of evidence varies (131, 150, 152). For instance, in interventions such as exercise, cognitive therapy and music-therapy, and individual tailoring of the intervention is absolutely necessary (116, 131, 150, 151). This is especially true for exercise-based pain management, in which the activities must consider the patients physical and cognitive abilities.

Pharmacological treatment of pain

The AGS recommendations state that when it comes to the pharmacological treatment of pain, the non-opioid analgesic paracetamol (or acetaminophen), with a maximum daily dose of 4 grams, is recommended (149). The use of Non-Steroid-Anti-Inflammatory drugs (NSAIDs) is only recommended with caution and in well-argued cases due to the high risk of harmful side-effects such as cardiovascular and renal side-effects. Guidelines for pharmacological pain treatment in older adults and

in NH patients are mainly based on the analgesic pain ladder, which was developed by the World Health Organization (WHO) for the purpose of treating cancer pain (153). At the bottom of the ladder, treatment with non-opioid analgesics such as paracetamol is found. If this is not sufficient, the addition of a weak opioid is considered, and if this is still not sufficient, treatment with a strong opioid orally, or transdermal/subcutaneously, for those unable to swallow pills is recommended (153). However, in older adults and in a frail NH population, step 2 of the ladder, including weak opioids such as tramadol, are well not well tolerated, thus this step is rarely used (149).

The AGS recommendations state that in patients with moderate to severe pain, reduced QoL due to pain, or functional impairment due to pain, the use of opioid analgesics should be considered (149). If patients suffer from pain on a daily basis, the goal should be to achieve a steady-state concentration of analgesics, so that pain is kept at a minimum throughout the day, meaning that long-acting opioids are preferred to short and intermediate acting opioids (149). The drugs morphine, oxycodone, buprenorphine and fentanyl are the most common strong opioids used, either as slow-release tablets, transdermal patches, or as short-release fast acting tablets for treatment of breakthrough pain (131, 149). For other types of pain, such as neuropathic pain, the use of adjuvant treatments, such as the antiepileptic drugs pregabalin and gabapentin, can be used (131, 149). Although guidelines recommend the use of opioid analgesics, they also state that their use should be closely monitored (131, 149). This is especially important to keep in mind when considering the current rise in opioid use, and their potential to cause harmful side-effects.

Systematic treatment of pain

To reduce the prevalence pain in a NH population, there is often a need for a systematic approach to pain assessment and treatment, as a study by Sandvik et al. from 2014 shows (154). In this cluster-randomized controlled trial (cRCT), the effect of a stepwise protocol for treating pain (SPTP) on pain scores in 352 NH patients with dementia and behavioral disturbances was investigated, and pain scores were

found to be reduced in the intervention group (154). In a more recent, smaller pilot-study, Brunkert et al. (2019) investigated the effect of a multilevel pain management intervention, comprising of staff-education and guideline implementation, on pain in 62 Swiss NH residents, and found that both self-reported pain and proxy-rated pain were reduced (155). A recent cRCT by Pieper et al. (2017), including 288 NH patients with dementia, demonstrated pain reduction in response to a multidisciplinary intervention including education in pain assessment and pain management (156). However, interventions that only include systematic pain assessment do not seem to ameliorate pain. This was shown by Rostad et al. (2018), who investigated the effect of regular pain assessments on pain in 112 Norwegian NH residents, and found no significant effect on pain scores or analgesic prescribing (157). A recent Cochrane review by Manietta et al. (2021) investigated if the addition of a pain-treatment algorithm reduced pain compared to education on pain treatment alone, and concluded that use of a pain-treatment algorithm had little to no effect in reducing pain score compared to education alone (158). However, the study populations varied significantly, and the authors recommended that the results be interpreted cautiously (158).

Analgesic use in people with dementia

In the NH population, the treatment of pain is complicated by dementia and other diseases which impact the recognition and assessment of pain; this puts patients at risk for undertreatment of pain (130). A recent systematic review by Griffioen et al. (2017), who investigated the use of opioid analgesics in people with cognitive impairment compared to people without cognitive impairment, found that people with cognitive impairment had a lower use of opioid analgesics than people without (159). There may, however, be a difference between the NH population and the home-dwelling population, as a study by Jensen-Dahm (2015) showed, where home-dwelling people with dementia were more likely to be prescribed an opioid analgesic, while NH patients with dementia were less likely to receive opioid analgesics than patients without dementia (160). Despite the risk of undertreatment, other studies may suggest an improvement in prescription policy in recent years. In 2011, Haasum

et al. investigated if there was a difference in analgesic prescription between people with and without dementia and found that people with dementia were more likely to receive paracetamol than people without dementia and as likely to receive other analgesics (161). In 2016, Sandvik et al. investigated the prescribing pattern of analgesic drugs in Norwegian NHs from 2000 to 2011, and found that up until 2009, PwD received fewer analgesics than people without dementia, while this difference disappeared in 2011 (162).

Consequences of opioid analgesics

The use of analgesic medications, and opioid analgesics in particular, are not exclusively positive (163). In recent years, there has been an increase in the use of opioid analgesics in NHs; in Norway the use of strong opioid analgesics has increased from 1.9% in 2000 to 17.9% in 2011 (162). Similar results were shown in a Swedish study of 4,933 NH residents by Hemmingsson et al. from 2018, where the use of opioid analgesics on a regular basis had increased from 19.6% in 2007 to 25.6% in 2013 (126). The same increase is obvious in the U.S. as shown in a study by Hunnicutt et al. (2018), where 32.4% of 315,949 NH patients were found to be prescribed opioid analgesics (164). One reason that the prescription of opioid analgesics to a NH residents can be troublesome is seen in its potential sedating side-effects, which makes older patients using opioid analgesics more prone to falls, and the following injuries such as fractures (165-167). There is also a possibility for potential harmful side-effects, due to interaction with psychotropic drugs, as shown by Erdal et al. who investigated the effect of pain treatment on depression in NH patients with dementia (168). They found that patients on antidepressants who were being prescribed a buprenorphine transdermal patch had a 23 times greater risk of dropping out of the study due to adverse events (168). As there seems to be an increase in the use of opioid analgesics, there is a need for better alternatives in pain treatment to reduce the use of opioid analgesics in those patients who benefit the most from them (150, 163).

2.7 Pain and NPS

2.7.1 Psychosis symptoms and pain

The relationship between pain and psychosis symptoms, has to this date not been extensively investigated. Pain is prevalent in NHs, and 40-60% of patients in NH suffer from pain daily (3, 169). Previous studies have shown that pain in PwD is associated with increased risk of delirium, as shown by Boltz et al. (2020), where they investigated factors associated with pain in 299 hospitalized patients with dementia (170). A similar result was found by Cheung et al. (2018), when they investigated clinical characteristics associated with the onset of delirium in 1,571 NH patients and found that the onset of delirium was significantly associated with pain (63). The association between pain and psychosis symptoms is, however, not thoroughly investigated with mixed findings in the few studies that are performed (Table 4).

In 1998, Cohen-Mansfield et al. investigated the relationship between psychosis symptoms and different demographics, and medical variables in 200 U.S. patients from adult day-care centers (171). The relationship between pain and psychosis symptoms were investigated, but neither delusion or hallucinations were found to be associated with pain (171). The same result was described by Kunik et al. (2005) who investigated the association of treatable comorbid conditions and the use of health care services in 99 U.S. veterans with dementia. Sub-analysis investigated the relationship between pain and psychosis symptoms but did not reveal any associations (172). However, two separate studies have found an association between pain and psychosis symptoms. A cross-sectional study by Tosato et al. (2012) investigated the association between pain and NPS in 2,822 cognitively impaired NH patients from seven European countries and found that pain and delusion were significantly associated. However, no association between pain and hallucinations were identified (80). Another retrospective 1-year cross-sectional study by Atee et al. (2020) included 479 Australian NH patients with dementia, who were referred to a national BPSD-service, and found that pain was significantly associated with hallucinations, but not delusions (173). All studies are described in table 4.

A matter that complicates the relationship between pain and psychosis symptoms is the fact that opioid analgesics may cause psychosis symptoms, such as hallucinations, as a drug side-effect. The pathophysiology is not fully understood, but as opioids have anticholinergic side-effects, psychosis symptoms can arise; however, one common hypothesis is opioid-induced dopamine dysregulation (66, 174). A review by Sivanesan et al. who investigated opioid-induced hallucinations found that the most common opioid associated with hallucinations is morphine, although fentanyl, buprenorphine and oxycodone have also been found to cause hallucinations (174).

2.7.2 Pain and other neuropsychiatric symptoms

Pain has been found to be associated with different NPS, with the strength of association varying between different studies (8, 78). A systematic review by van Dalen-Kok et al. (2015) investigated the association between pain and NPS, and found the strongest association between pain and depression, followed by pain and agitation (78). Similar results were identified by Atee et al. (2020) who highlighted the association between pain and agitation, in addition to depression, aberrant motor behavior, apathy, irritability and appetite disturbances (173). Due to these associations, it would be reasonable to think that pain treatment would reduce NPS as well as pain in PwD.

Table 4: The association between pain and psychosis			
Author (year), country	**Population**	**Assessment instruments**	**Findings**
Atee et al. (2020), Australia	N = 479 NH patients with dementia, who were unable to communicate their own pain, and who were referred to the national support-service for BPSD-treatment.	**Psychosis symptoms:** Neuropsychiatric inventory **Pain:** Artificially intelligence-based pain assessment tool (PainCheck). Rates pain as no pain, mild, moderate or severe pain.	Hallucinations associated with pain (OR: 1.75, p = 0.035)
Tosato et al. (2012), Czech Republic, England, Finland, France, Germany, Italy and The Netherlands	N = 2 822 NH patients with cognitive impairment.	**Psychosis symptoms:** interRAI instrument for long term care facilities (interRAI-LTCF). Delusion and Hallucinations assessed as present or not. **Pain:** interRAI-LTCF. Pain in the last 3 days divided in 3 groups: No pain, mild pain, and moderate to excruciating pain.	Delusions associated with moderate to excruciating pain (OR: 1.73, 95% CI: 1.21 – 2.45), but not mild pain. No associations between pain and hallucinations.
Kunik et al. (2005), U.S.	N = 99 Community-dwelling people with dementia who regularly visited the department of veteran affairs (VA) in Houston, U.S.	**Psychosis symptoms:** Neuropsychiatric Inventory **Pain:** Modified Philadelphia geriatric center pain intensity scale – Pain during the last week rated from 1 (no pain) to 6 (worst pain possible).	No association between pain and psychosis symptoms as a group (Pearson correlation: 0.15, p >0.05)
Cohen-Mansfield et al. (1998), U.S.	N = 200 Community-dwelling people with and without dementia who regularly visited adult day-care centers in Maryland, U.S.	**Psychosis symptoms:** Behavioral pathology in Alzheimer's disease rating scale (BEHAVE-AD) **Pain:** Short form of the McGill Pain Questionnaire – Pain rated from a scale from 1 (no pain) to 6 (excruciating pain)	No association between pain and delusion, or pain and hallucinations

One of the first studies was by Manfredi et al. (2003), who in a placebo-controlled cross-over trial, investigated the effect of opioid analgesics on agitation in 47 NH patients with dementia, and found no significant effect on agitation for the total population (175). Chibnall et al. (2005), performed a randomized double blind, placebo-controlled cross-over trial, investigating if treatment with paracetamol would reduce behavioral symptoms in 25 NH patients with dementia (176). No effect on agitation was observed, but a positive effect on social activities was seen (176). The largest cRCT to date, the PAIN.BPSD study by Husebo et al. (2011) investigated the efficacy of a SPTP on behavioral disturbances (177). In this trial, agitation was significantly reduced in the intervention group compared to the control group (177). A sub-analysis from the same study later showed that mood-symptoms, such as depression, apathy, sleep disturbances, and appetite disturbances also improved (79).

In a more recent study, Erdal et al. (2018) investigated the effect of analgesic treatment on depression in NH patients with dementia, in a multicenter double-blind placebo-controlled trial (DEP.PAIN.DEM) (178). There was no significant intervention-effect by pain treatment, and as opposed to the treatment group, depression was reduced in the placebo group (178). A sub-analysis from the same study found that sleep-disturbances were significantly reduced in the treatment group (179). However, inclusion criterium was depression and not pain for the DEP.PAIN.DEM study. The latest study to date, which investigates the effect of pain treatment on NPS was conducted by van Dam et al. (2020) (180). They investigated the effect of paracetamol on QoL, pain and NPS including psychosis symptoms, through a randomized double-blind placebo-controlled cross-over trial, and found no significant treatment effect on neither QoL nor any NPS (180). The study by van Dam et al. is the only other study, to date, that has investigated the effect of pharmacological pain treatment on psychosis symptoms.

2.8 The rationale of this thesis

Psychosis symptoms in NH patients have negative consequences not only due to the distress they cause, but also through the potential harmful consequences psychotropic medication use can cause. There is a great need to discover potential underlying causes of psychosis symptoms, which can be treated rather than the symptoms themselves. Previous literature suggest that pain may be one of these factors. There are only a few studies that investigate this phenomenon, and in these studies the psychosis symptoms are only secondary outcomes. In this thesis, I hope to contribute with solid knowledge on both the characteristics of NH patients with psychosis symptoms and potential underlying causes for psychosis, as well as the relationship between pain, pain treatment and psychosis symptoms. If such a relationship is established in NH patients, psychosis treatment decisions should be revised to include pain assessment and treatment in this population.

3. Aims of the thesis

The overarching aim of this thesis is to investigate the relationship between pain and the psychosis symptoms delusion and hallucinations, both as individual symptoms and as a symptom cluster, and how these symptoms are impacted by pain treatment. This will be conducted on the basis of both cross-sectional and longitudinal method approaches. The thesis also explores the characteristics of people with psychosis symptoms and any potential treatment options to identify underlying factors that may trigger psychosis symptoms.

Paper 1:

- Investigate the efficacy of pain treatment on agitation and psychosis symptoms in NH patients with dementia.
- Investigate the association between pain, agitation and psychosis symptoms.
- Investigate whether the prescription of opioid analgesics increases the likelihood of psychosis symptoms.

Paper 2:

- Investigate the characteristics of NH patients with psychosis symptoms.
- Investigate how the use of antipsychotic medications impact residents with psychosis symptoms.
- To identify potential underlying factors associated with psychosis symptoms in NH residents.

Paper 3:

- Investigate the effect of a multicomponent intervention on both pain and psychosis symptoms.
- Investigate the effect of a multicomponent intervention on the prescription of opioid analgesics.
- Investigate the relationship between pain and psychosis symptoms over time.

4. Methods

In the method section I will describe the two different trials on which this thesis is based. The Pain-BPSD trial, which is the data source for the first paper, and the COSMOS trial, which is the data source for papers 2 and 3. These trials will be described separately in each part of the method section: Data sources, Participants, Intervention, Outcome Measures, Statistics, and Ethics and Study Registration.

4.1 Data Sources:

Pain-BPSD trial: As the potential relationship between pain and psychosis is complex, it was important to investigate not only how these symptoms were associated, but also how pain treatment affected psychosis symptoms. To investigate this, there was a need to include a population with a high number of people experiencing psychosis symptoms. The Pain-BPSD trial is suggested as appropriate because of the inclusion of NH patients with dementia experiencing behavioral disturbances. The coexistence of psychosis symptoms and other NPSs increase the likelihood of identifying this group of interest.

The COSMOS trial: To investigate the characteristics of NH patients with psychosis, and to investigate the relationship between pain and psychosis symptoms over time, there was a need for a more generalized NH population to secure that the results were representable for a broader population. The COSMOS-trial, which included all NH patients ≥65 years, and a life expectancy >6 months, ensured a broad and diverse NH population, making the findings representable for most NH patients.

4.1.1 Paper 1: The Pain-BPSD trial

The Pain-BPSD study was a cRCT, with the primary aim of investigating the effect of individualized pain treatment according to a SPTP on agitation in NH patients with dementia (177). Each individual NH unit was defined as a cluster and randomized to either intervention or treatment as usual. The intervention lasted for 8 weeks with a wash-out period off 4 weeks. The clustered design was done to avoid contamination

by caregiver-staff who cannot be expected to treat individual patients in a unit in different ways. Randomization was conducted by a statistician using a generated list of random numbers allocated to each cluster, using Stata version 8. The Pain-BPSD trial was performed from October 2009 to June 2010 and was a multicenter study that included 18 NHs from 5 different municipalities in Western Norway. Data collection for all patients was done by two research assistants who received special training in the use of the assessment instruments and were blinded for group allocation. Assessments were made by interviewing each patient's primary caregiver (proxy-rater) and reviewing the medical records for patients' characteristics. Assessments were conducted at baseline, week 2, 4, 8 and 12. The intervention process was done by research assistants and nurses who did not take part in the assessments.

4.1.2 Paper 2 and 3: The COSMOS-trial

The COSMOS-trial was a multicenter multicomponent cRCT intervention-trial, with the primary aim of improving NH patients QoL (1). The COSMOS-acronym represents COmmunication, Systematic assessment and treatment of pain, Medication review, Organization of activities and Safety. This symbolized the five main components that made up the COSMOS-intervention. The COSMOS-intervention based itself on current state of the art knowledge on best practice within the five main components (86, 137, 181-183) and combined them into a single multicomponent complex intervention that implemented knowledge and practical interventions in the NH-unit to improve the patients QoL.

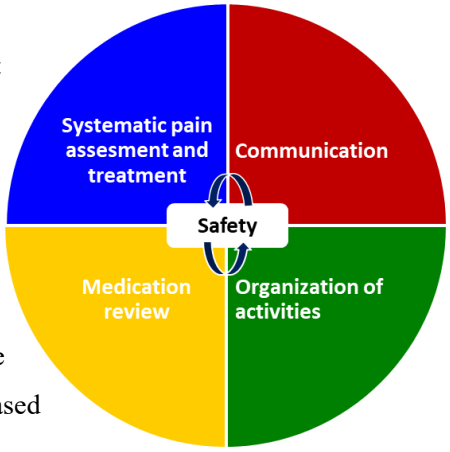


Figure 1: The COSMOS-logo including all five main components

The COSMOS-trial was performed from May 2014 to December 2015 and included 33 NHs from 8 different Norwegian municipalities. Comparable to the Pain-BPSD trial, each individual NH unit was defined as a single cluster and randomized to either the COSMOS-intervention or care as usual. The cluster design was chosen to avoid

contamination between units, i.e., the risk that components of the intervention are adopted by staff in units that was randomized to not receive the intervention. Randomization was done as a constrained complete list randomization, and randomization was stratified according to the 33 different NHs to ensure as equal distribution of geographical factors and monetary status as possible.

I joined the COSMOS-team in January 2014 and was a part of the research team led by Professor Bettina S. Husebo (BSH) and Professor Elisabeth Flo-Groeneboom (EFG). The team consisted of 2 PhD-candidates, Irene Aasmul (IA) and Christine Gulla (CG), a fellow medical student, Tony Elvegaard (TE), and me. Along with IA, CG and TE, I contributed to the implementation process, performed the data collection, and oversaw the follow-up of all participating NH-units. Assessments were done at baseline, month 4 and month 9. The entire study-protocol has previously been published in full (1), and this thesis includes the main elements most relevant to the three articles included in this thesis.

4.2 Participants

4.2.1 Pain-BPSD trial (Paper 1)

The Pain-BPSD trial included 60 NH units; 920 patients were screened for dementia, and 420 people with moderate or severe dementia were identified. From these, 68 were excluded, leaving 352 patients to be randomized.

Inclusion Criteria:

- Patients ≥65 years, residing at the NH for at least 4 weeks prior to inclusion.
- Dementia according to the Diagnostic and Statistical Manual of mental disorders – 4th edition (DSM-IV).
- Functional Assessment Staging Tool (FAST) score >4. (184)
- MMSE score ≤20 (185).
- A Cohen-Mansfield Agitation Inventory (CMAI) score ≥39, representing clinically relevant behavioral disturbances (186).

Exclusion criteria:

- Severe medical disease with expected survival <6 months at time of inclusion.
- Severe neurological (e.g., Huntington disease) or psychiatric (e.g., schizophrenia) disease.
- Severe aggression (Neuropsychiatric Inventory – NH version score ≥8) with aggression as the predominant symptom.
- Severe hepatic or renal failure.
- Known allergy to one of the study-medications.
- Anemia with a hemoglobin concentration <8.5 mmol/L.

4.2.2. The COSMOS-trial

The study enrolled 72 NH units and 765 patients from the municipalities: Bærum, Sarpsborg, Bergen, Øygarden, Sund, Kvam, Askøy and Fjell. From these, five NH units were excluded: Two due to the units being short-term units, two due to change of NH managers, and one due to participation in another trial. This left 67 NH units to be randomized.

Inclusion criteria for the trial:

- Patients ≥65 years old, residing at the NH for at least two week prior to inclusion.
- Patients who moved to the unit within two months after the start of the trial were also included.

Exclusion criteria for the trial and paper 3:

- Patients with a life-expectancy <6 months.
- Patients with schizophrenia.

Additional exclusion criteria for paper 2:

- Patients who did not complete the NPI-NH assessment at baseline.

4.3 Intervention

4.3.1 Pain-BPSD trial

The patients who were allocated to the intervention received individual pain treatment according to a SPTP, which was developed in accordance with the recommendations by the AGS in 2009 (149). A team consisting of 2 people from the research team, an anesthesiologist (BSH) and a registered nurse (Reidun K. Sandvik), the NH physician of each of the included NHs, and the patient's primary caregiver, discussed each individual patient allocated to the intervention group, and through a thorough discussion based on the patient's situation and current treatment decided on which step of the SPTP the patient should be started on. The treatment protocol and allocation of patients to each step is described in table 5.

Table 5: Treatment protocol for the pain-BPSD study

Step	Treatment baseline	Study treatment	Dosage
1	No analgesics/Low dose paracetamol	Paracetamol	Max 3g/day
2	Max dose paracetamol/low dose morphine	Morphine (Dolcontin®)	5mg x2/day Max: 10mg x2/day
3	Buprenorphine low dose/unable to swallow tablets	Buprenorphine transdermal patch (Norspan®)	5µg/h Max: 10µg/h
4	Neuropathic pain	Pregabaline (Lyrica®)	25mg x1/day Max: 300mg/day

The intervention period lasted for 8 weeks, followed by a 4-week wash-out period, in which the pain medication was reverted to the prescription at baseline. If patients did not tolerate the study medication, dose-reduction was attempted, or the patient was withdrawn from the study, and treated as deemed appropriate by the NH physician. Use of analgesics as needed was permitted and monitored during the whole study both in the intervention and the control group. Physicians treating patients in the control-group were encouraged to keep prescription in the control group unchanged during the study period if possible.

4.3.2 The COSMOS-trial

The COSMOS-intervention included five different "sub-interventions" called the five components of the COSMOS-trial, put together into a single, complex, multicomponent intervention. Four of the components were defined as "active components". These four of the components were designated its own color (see the COSMOS figure) to be used in all the educational material received by the care-workers at the NH. Safety, the fifth component, was included in all the 4 active components, as focus on increased patient safety was important for every intervention done in the COSMOS-trial. The following is a summary of 4 of the active intervention-components from the COSMOS-trial (1).

Communication (red color):

NHs were trained in and encouraged to implement a systematic approach of advance care planning (ACP) in the NH. ACP is an ongoing communication and decision-making process with patients and relatives, addressing the approaching death and practical challenges regarding ethics, treatment, and care, well before the patient reaches a critical state (181). The COSMOS-trial components focused on future decisions on the treatment of the NH patient, their wishes, values, and goals for the NH stay (181). Optimally, the discussion and decisions are based on the patient's beliefs, values, wishes and past decisions. Included NHs were encouraged to have a meeting within the first 2-3 weeks after the patient's admission to the NH. Telephone contact with closest relatives at least once a month was encouraged. Contact was also encouraged whenever the patients' medical situation changed, and after hospitalizations (1, 187).

Systematic Assessment and treatment of pain (blue color):

In the COSMOS-trial NH staff were trained in the use of the pain assessment tool MOBID-2 and encouraged to perform pain assessment at least twice a year, and every time chronic or acute pain is suspected. Staff was also recommended to conduct a pain assessment before, and 2-4 days after, initiation of pain treatment, as well as a

follow-up assessment 8-12 weeks after initiation. NH staff were also trained in the use of a SPTP in pain treatment (1).

Medication review (yellow color)

The staff received education in the use of different guidelines for the use of various medications in treatment of elderly NH patients. Each NH received a visit from two physicians from the COSMOS-team, BSH and CG, to assist and guide physicians and nurses in a medication review of their patients (1, 188).

Organization of Activities (green color):

Education on the potential benefits of activities in NH patients, and what type of activities that provide the most benefit. Education in the development of individualized activity plans for each NH patient (1).

Implementation process

The COSMOS-intervention was implemented beginning with a 2-day educational seminar, where each NH unit was obligated to participate with at least two staff members, usually registered nurses, or licensed practical nurses, who were named as COSMOS-ambassadors. The ambassadors had the responsibility to implement the knowledge from the educational seminar in their respective NH unit (cluster). In addition, all NH managers and physicians were invited to participate. Each of the main components had approximately 2.5 hours of the education seminar designated to them. Education was done both through lectures, role-play, patient centered discussion, and case-solving. Each NH unit received educational material, such as guidelines, power-point handouts, flashcards, flyers, and a poster to better promote and implement COSMOS in their own unit. All NH units received individual patient-logs to document the degree of the implementation. In these logs they could e.g., register if the patient received pain assessment, and if any treatment measures were taken, if medication reviews were performed, if they participated in any organized activities etc. Each week the COSMOS-ambassadors were encouraged to designate a specific color to represent the main topic to focus on: red for communication, blue for

pain, etc. The ambassadors were responsible to teach the other care-workers at the NH unit to implement the knowledge and practice as good as possible. The four members of the COSMOS-team, TE, CG, IA, and myself, had bi-weekly telephone-contact with the COSMOS-ambassadors at the intervention units to help with the implementation and to offer guidance on any problems the NH should encounter concerning implementation. The NHs were also given contact information to the COSMOS-team so that they could contact us at any time. A midway seminar was held after two months where the COSMOS-ambassadors could meet and discuss any problems they had encountered, as well as receive feedback on how they could solve them.

The intervention period lasted for 4 months. After this period, the COSMOS team contacted the NHs once a month to follow up any queries the NHs should have regarding the study.

Control group:
The control group were told that they were on the waiting list to receive the COSMOS-intervention and received care as usual during the first 9 months. After the COSMOS-trial was completed, they received the same education-seminar that the intervention units received. They were trained in the use of each assessment instrument, including the use of the MOBID-2 Pain Scale.

4.4 Outcome measures

Behavioral disturbances measured with the CMAI was the primary outcome in the Pain-BPS trial. In the COSMOS-trial, QoL was the primary outcome. Papers 1-3 are therefore based on secondary outcome measures.

4.4.1 Neuropsychiatric Inventory Nursing Home version

The primary outcome for the 3 papers in this thesis (i.e., not the primary outcome of the trial) was the NPI-NH, which assesses the frequency, intensity, and caregiver distress for 12 neuropsychiatric symptoms: Delusion, Hallucination,

Agitation/Aggression, Depression, Anxiety, Apathy, Euphoria, Disinhibition, Irritability, Aberrant Motor Behavior, Sleep and Appetite Disturbances (189, 190). The symptom frequency (F) is measured on a scale from 0 to 4, where 0 represents not present and 4 represents present daily. The symptom severity (S) is measured on a scale from 1 to 3, where 1 represents a mild symptom with little strain on the patient, while 3 represents a severe symptom with much strain on the patient. The two scores (FxS) are then multiplied to gain a score for each symptom, ranging from 0 to 12. A symptom with a score ≥4 is suggested as a clinically significant symptom (4, 191).

These neuropsychiatric symptoms can also be clustered according to their co-existence, earlier described by Aalten et al., Selbaek et al., and Cheng et al. (Table 1) (45, 47, 48). In our studies, we utilized the factor analysis performed by Cheng et al. (2012), which puts delusion and hallucinations together in a psychosis cluster, and aggression, irritability, disinhibition, and aberrant motor behavior together in an agitation cluster (48). Since euphoria does not consistently co-occur with any of the other symptoms in different factor analysis it was combined with delusion and hallucinations in the psychosis cluster in paper 1. Here we followed the findings by Selbaek et al. (2012), who highlighted that euphoria most often co-occurred with delusion and hallucinations (45). We left this structure in the papers 2 and 3 due to the low prevalence of euphoria in this dataset. Thus, the difference in range of the total score for the psychosis cluster is due to this choice (Paper 1: 0-36, Paper 2 and 3: 0-24). The scores in the agitation cluster have a range from 0 to 48.

4.4.2 The MOBID-2 Pain Scale

The secondary outcome in all three papers is the MOBID-2 Pain Scale, developed by Husebo et al. (140, 141). It consists of part 1 and part 2. In part 1, potential pain is rated during five active guided movements. For each movement, raters who know the patient well are encouraged to observe the patient for any signs of pain, and then rate the patient's pain on a NRS from 0 to 10, where 0 represents no pain, and 10 worst pain imaginable. Part 2 consists of 5 items, assessing pain that might be related to the head, skin, and internal organs, based on observations from the last week. All items

are rated on a NRS from 0-10. After completing all 10 items, raters are encouraged to rate the patient's total pain, taking all items into account, on a NRS from 0-10 (141). The tool is thoroughly tested for validity and reliability, and is one of the few pain assessment tools that are tested for responsiveness, meaning its ability to assess change in pain after treatment has been initiated (142). A total score ≥3 is viewed as a clinically significant pain score, which requires contact to the NH physician and probably non-pharmacological and/or pharmacological treatment of pain (140-142).

4.4.3 Quality of life

The QoL was assessed using two different assessment tools. The Quality of Life in Late stages In Dementia (QUALID), which was developed by Weiner et al. (2000). QUALID includes 11 different items (range: 1 to 5), which can be summed to a total score (range: 11 to 55), where a lower score indicates better QoL (192). The second measurement tool was the Quality of Life in Dementia (QUALIDEM), which assesses 40 different items on a scale from 0 to 3, giving a total score ranging from 0 to 120, where a higher score indicates better QoL (193). For the QUALIDEM an 18-item short-version exists, because some items rely on the patient's communication ability and are not applicable for all people with advanced dementia. We therefore utilized the short version with total range of 0 to 54 to guarantee the applicability for all participants (193).

4.4.4 Other measurement tools

Depression was assessed by the Cornell Scale for Depression in Dementia (CSDD). The tool includes 19 items, where scores range from 0: not present to 2: severe, giving a range from 0 to 38 (194). Cognitive function was measured using the mini mental state examination (MMSE), where a person goes through 30 questions/tasks, rated as approved or not approved, giving a range of 0 to 30 (185). NH patients functional dependence was assessed using the functional assessment staging (FAST), which ranges from 1 to 7, where 1 represents functionally independent, and 7 represent total dependency (184). Agitation was assessed using the Cohen-Mansfield agitation inventory (CMAI), where agitation is rated through 29 items, each item

ranging from 1: never to 7: several times each hour, giving a range of 29 to 203 (186). Personal activities of daily (P-ADL) living were assessed using the Lawton and Brody's ADL tool, where people's ability to perform ADL tasks is rated through 6 items, with each item ranging from 0: not applicable and 1: no problem performing the activity to 5: unable to perform the activity, giving a range of 0 to 30 (195). Table 6 summarizes all tools used in papers 1-3.

Table 6: Instruments

Instrument	Paper 1	Paper 2	Paper 3
NPI-NH	D, MR	D, MR	D, MR
MOBID-2	D, MR	D, MR	D, MR
CSDD		D, MR	D, MR
CMAI	D	D	D
ADL	D	D, MR	D
MMSE	D	D, MR	D, MR
FAST	D	D	D
QUALIDEM		D, MR	
QUALID		D	MR

D: Used to describe the study population, MR: Used in main results

4.4.5 Medications

The information regarding the patient's medication was collected from the patients' medical records.

Analgesics

Analgesics were mainly divided into two different groups according to the ATC-registry: the non-opioid analgesics, as defined as the groups N02B and N02C in the ATC registry, and opioid analgesics as noted N02A. Analgesics as a combined group was noted as N02 in the ATC-registry. The use of NSAIDs noted as M01 and M02 was included in paper 1.

Psychotropic drugs

Psychotropic drugs were defined differently in papers 1 and 2, and paper 3. In paper 1 and 2, psychotropic drugs as a group include antipsychotic drugs (N05A), anxiolytics

(N05B) and Hypnotics and Sedatives (N05C). In paper 3, antidepressants (N06A) and anti-dementia drugs (N06D) were included in the psychotropic drug category.

4.5 Statistics

All statistical analyses were performed by the author of this thesis in collaboration with the statisticians Dagrunn Daltveit Slettebø (paper 1 and 2) and Janne Mannseth (paper 3).

4.5.1 Paper 1

For baseline characteristics, differences between the control and intervention group were analyzed using an independent sample t-test for normally distributed variables, a Chi square test for categorical variables and a Mann-Whitney U-test for non-normally distributed variables. For associations between NPS and pain, binary logistic regression was used, where a clinically significant NPS represented the dependent variable, while the total MOBID-2 score represented the independent variable. Associations were adjusted according to age, gender, dementia severity and ADL-function. The intervention effect on NPS were analyzed using the Mann-Whitney U-test on the difference in NPI-NH change between the intervention and control group. The association between opioid analgesics and psychosis symptoms were assessed using binary logistic regression. All statistical analyzes were done using the Statistical Package for Social Sciences (SPSS) version 22.

4.5.2 Paper 2

Patients with one or more psychosis symptoms at baseline were compared with patients without psychosis symptoms. The difference in characteristics between patients with and without psychosis, and with and without antipsychotic medication, were analyzed the same way as differences in baseline characteristics in paper 1. The associations between psychosis symptoms, defined as a clinically significant symptom, and other factors such as number of medications and pain, defined as clinically significant pain (MOBID-2 $\geq$3), were investigated using binary logistic regression with robust standard error estimation to adjust for clustered design.

Psychosis symptoms both as a group and individually were defined as dependent variables, and potential associated factors were defined as independent variables. Associations were adjusted according to age, gender, dementia diagnosis and cognitive functioning (MMSE-score). Analyses were done using SPSS version 23 and Stata version 15.0.

4.5.3 Paper 3

The differences in baseline characteristics between the control and the intervention group were investigated using the same statistical methods as in papers 1 and 2. The intervention effect on pain and psychosis symptoms were investigated using mixed effect linear regressions, with random intercept for clusters and time as a categorical variable. The association between psychosis symptom and pain, as defined as clinically significant pain (MOBID-2 ≥3), were done using mixed effect logistic regression, with maximum likelihood estimation and random intercept for clusters. A clinically significant psychosis symptoms as a group and individually were defined as the dependent variable, and pain as the independent variable. Associations were adjusted for the effect of time, age, dementia severity, and use of opioids. Model fit was associated using the Akaike information criterion (196). Difference in characteristics of patients with or without pain, and using or not using analgesics, were analyzed using ANOVA with Bonferroni correction for repeated analyses.

4.6 Ethics and study registration

4.6.1 Pain-BPSD trial

For patients who were able to understand the possible risks and benefits of the study, informed consent was obtained. If possible, informed consent was obtained with a next of kin present. When the patients were not able to provide an informed consent, due to reduced cognitive abilities, a presumed consent was obtained from a next of kin or legal guardian, with the patient present if possible. Both the patient, their next of kin or their legal guardian, were informed that they could withdraw from the study at any point in time. The study was approved by the Regional Ethical Committee of Western Norway for Medical and Health Research (REK-Vest 248.08) and is

registered at clinicaltrials.gov (NCT01021696) and at EudraCT (EudraCTnr: 2008-007490-20).

4.6.2 COSMOS-trial

Patients who were able to understand the information regarding the COSMOS-trial, and its potential risks and benefits, provided informed consent. When the patients were not able to provide an informed consent, due to reduced cognitive abilities, a presumed consent was obtained from a next of kin or legal guardian, after explaining the study procedure and the potential risks and benefits to them, with the patient present if possible. The patient, as well as their next of kin, or legal guardian, were all informed that they could withdraw from the study at any point in time, without providing a reason for doing so. The COSMOS-trial was approved by the Regional Ethical Committee of Western Norway for Medical and Health Research (REK 2013/1765) and registered at clinicaltrials.gov (NCT02238652).

5. Main Results

5.1 Paper 1

Habiger TF, Flo E, Achterberg WP, Husebo BS: The Interactive Relationship between Pain, Psychosis, and Agitation in People with Dementia: Results from a Cluster-Randomized Clinical Trial. Behavioral Neurology 2016; 2016:8

- Three-hundred and fifty-two patients from 60 NH units were included in the final study sample, where 175 patients were cluster-randomized to the intervention group, and 177 patients to the control group.
- The average MOBID-2 score was 3.7 (SD: 2.5) in the control group and 3.8 (SD: 2.7) in the intervention group. Seventy-one patients (20.2%) in the control group, and 83 patients (23.6%) in the intervention group, had at least one clinically significant psychosis symptom at baseline.
- There was an association between total MOBID-2 score and disinhibition (OR: 1.21, 95% CI: 1.10-1.34, $p < 0.001$), and between pain and irritability (OR: 1.10, 95% CI: 1.01-1.21, $p = 0.032$). No association between total MOBID-2 score and any psychosis symptoms were found.
- The intervention significantly reduced agitation compared to the control group, with a mean difference (MD) of -4.9, $p < 0.001$. A significant intervention effect was also seen for the individual symptom's aggression (MD: -1.8, $p = 0.001$) and aberrant motor behavior (MD: -1.2, $p = 0.017$).
- No significant intervention effect on the psychosis cluster (MD: -1.1, $p = 0.091$ was found for the total population. A significant intervention effect on the psychosis cluster (MD: -1.7, $p = 0.034$) and delusion (-1.6, $p = 0.031$) was found in patients who experienced at least one symptom of psychosis at baseline.
- No association between the use of opioid analgesics and the prevalence of delusion (OR: 0.96, 95% CI: 0.56–1.65) or hallucinations (OR: 0.69, 95% CI: 0.34–1.41) was found at baseline.

5.2 Paper 2:

Habiger TF, Achterberg WP, Flo E, Husebo BS: Psychosis symptoms in nursing home residents with and without dementia-Cross-sectional analyses from the COSMOS study. Int J Geriatr Psychiatry 2019;34(5):683-691

- Seven-hundred and twenty-three patients were screened for inclusion, and 178 were excluded, leaving 545 patients from 67 NH units to be included in the COSMOS-trial. Of those, 512 patients completed the baseline assessment of the NPI-NH and were included in the analyses in paper 2.
- One-hundred and twelve patients (21.9%) had at least one clinically significant symptom of psychosis. Ninety-four patients had a clinically significant delusion (18.4%) and 45 (8.8%) had clinically significant hallucinations.
- Patients with psychosis symptoms had lower cognitive functioning as measured with the MMSE (MD: 2.8, $p < 0.001$), lower QoL according to the QUALIDEM scale (MD: 8.5, $p < 0.001$), higher depression scores on CSDD (MD: 6.8, $p < 0.001$), higher total scores on the NPI-NH caregiver distress (MD: 10.8, $p < 0.001$), and lower ADL-functioning (MD: 1.7, $p = 0.003$).
- Compared to patients with psychosis symptoms not using antipsychotic medication, patients with psychosis symptoms who were prescribed an antipsychotic had lower QoL (MD: 5.5, $p = 0.005$) as measured by the QUALIDEM-tool.
- In the association-analyses, psychosis symptoms as a group were associated with clinically significant pain (OR: 3.19, 95% CI: 1.94-5.24, $p < 0.001$), lower QoL (OR: 0.89, 95% CI: 0.86-0.92, $p < 0.001$), higher number of prescribed drugs (OR: 1.10, 95% CI: 1.03-1.17, $p = 0.005$, and sleep disturbances (OR: 4.51, 95% CI: 2.91-6.99, $p < 0.001$). The same associations were found for the individual symptoms of delusion and hallucination.

5.3 Paper 3

Habiger TF, Achterberg WP, Flo E, Mannseth J, Husebo BS: Managing pain and psychosis symptoms in Nursing Home patients: Results from a cluster-randomized controlled trial (COSMOS). J Am Med Dir Assoc 2021;22(8):1692-8.

- Of the 545 patients and 67 NH units included in the COSMOS-trial, 297 patients and 36 NH units were allocated to the intervention group, while 248 patients and 31 units were allocated to the control group.
- Clinically significant pain (MOBID-2 ≥3) was found to be longitudinally associated with both psychosis symptoms as a group (OR: 2.03, 95% CI: 1.19-3.45, p = 0.009) and delusion individually (OR: 2.12, 95% CI: 1.23 – 3.63, p = 0.007). No longitudinal association was found between pain and hallucination.
- Patients using antipsychotic medications were more likely to experience pain (OR: 1.78, 95% CI: 1.02 – 3.10, p = 0.043) than patients not using antipsychotic medication.
- The COSMOS-intervention did not have a significant effect on pain as measured by the MOBID-2 total score (β: -0.23, 95% CI: -0.88 – 0.42, p = 0.49) in the total NH population from baseline to month 9. In PwD, a significant intervention-effect on musculoskeletal pain, as measured by the MOBID-2 part 1, was found (β: -0.45, 95% CI: -0.90 – -0.01, p = 0.047) from baseline to month 9.
- There were no significant intervention effect on the psychosis cluster from baseline to month 9 (β: 0.23, 95% CI: -0.92 – 1.37, p = 0.70), or the individual symptoms delusion (β: 0.19, 95% CI: -0.57 – 0.96, p = 0.62) and hallucinations (β: 0.01, 95% CI: -0.58 – 0.59, p = 0.98).
- The number of patients being prescribed regular opioid analgesics were 31.5% in the control group and 30% in the intervention group. The number increased to 38% baseline to month 9 by 38% in the control group and to 35% in the intervention group. There was no significant intervention effect on the prescription of opioid analgesics (OR: 0.95, 95% CI: 0.53 – 1.70, p = 0.86)

Figure 1: Characteristics of the COSMOS and Pain-BPSD-trial

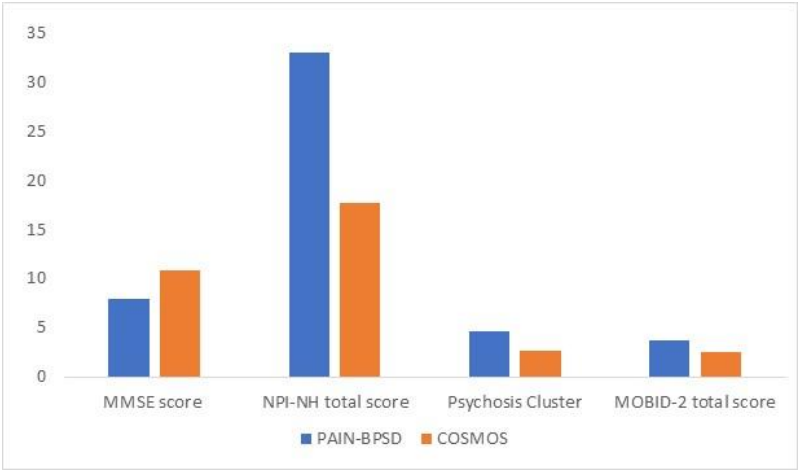
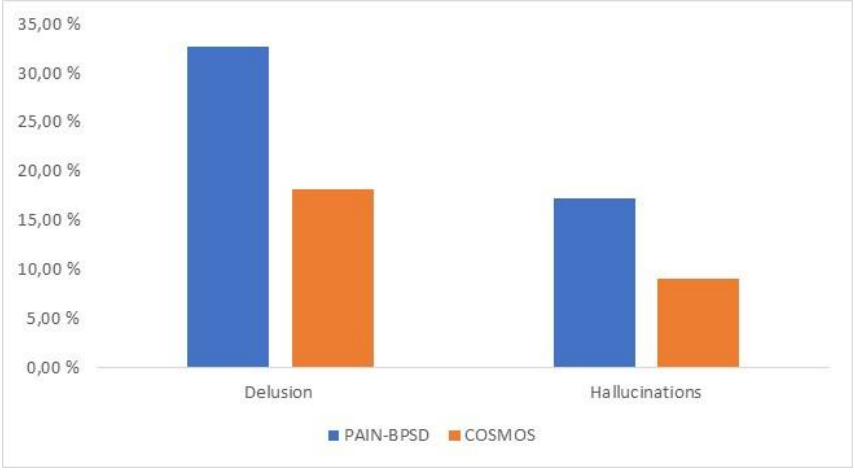


Figure 2: Number of patients experiencing psychosis symptoms



6. Discussion

6.1 General Considerations

The overarching aim of this thesis was to investigate the relationship between pain and psychosis symptoms in a Norwegian NH setting, and how pain management may affect psychosis symptoms. Paper 1 was based on secondary analyses and mainly focused on the effect of pain treatment on NPS. It used data from a cRCT, the Pain-BPSD trial. Papers 2 and 3 were secondary analyses from a large complex multicomponent cRCT, the COSMOS-trial. The papers varied in their methodology in that paper 2 used a cross-sectional design, while paper 3 is a combination of a prospective cohort design and an intervention-study.

Paper 1 focused on the pharmacological management of pain and how it affected behavioral disturbances in NH patients with dementia. To reduce the risk of adverse events, the inclusion and exclusion criteria were stringent, perhaps reducing the generalizability of the study-results on the expense of patient safety. However, patient safety should always be the focus when designing a trial, and narrow inclusion and exclusion criteria were a necessary step to ensure that this was the case. The cRCT design, the gold-standard for clinical trials performed in real world institutions, provides a solid foundation for interpretation of the results, although the lack of placebo needs to be taken into consideration.

Papers 2 and 3 used data from the COSMOS-trial to investigate the characteristics of NH patients with psychosis symptoms, the relationship between pain and psychosis symptoms and the effect of a complex multicomponent intervention on both pain and psychosis. The use of a mainly unselected group of NH patients has both its positive and negative sides. It is positive in that the results can be viewed as applicable to a broader NH population; however, it is negative in that the number of patients with psychosis symptoms will be lower than, e.g., a sample of only NH patients with dementia, thus limiting the potential to draw a more certain conclusion of the association between pain and psychosis symptoms.

The effect of pain treatment on psychosis symptoms (Paper 1) should perhaps have been done after investigating the characteristics of NH patients with psychosis symptoms (Paper 2). This could have established an association between pain and psychosis symptoms before investigating the effect of pain treatment on them. The reason for this order was that the Pain-BPSD trial was already completed, and the data was readily available for analysis, while the COSMOS-trial was an ongoing trial, and data-collection due to be completed later.

Following this introduction, there will be a thorough and critical discussion regarding the use of research methodology, followed by a discussion of results and ethical considerations.

6.2 Methodological considerations

6.2.1 Paper 1

Study design

The use of a single-blind cRCT design seemed the most appropriate method for investigating the effect of pain treatment on NPS in NH patients with dementia. The randomized-controlled trial design is viewed as the gold standard in clinical research for testing the effect of a certain treatment on a patient outcome (197). An argument could be made that randomization should occur at the individual level rather than the cluster-level; however, in a NH-setting, this would be impractical, and would most likely reduce the study's validity severely. The reason for this is how a NH unit is organized, where a team of care-workers, including nurses, are responsible for daily care and treatment of all the patients in the unit. If individual patients were to be randomized, then the care-workers would be expected to treat individual patients differently, as the intervention was systematic assessment and treatment of pain. It would be unreasonable to think that the knowledge acquired by the nurses treating the patient would not "bleed over" to the patients acting as controls from the same NH unit, thereby altering usual treatment, which acted as the control condition.

Internal Validity

The internal validity of a study refers to at what degree a difference observed between two groups of patients is due to a true difference between them, and not due to other causes such as different types of bias or due to chance (198). In order to achieve a strong internal validity, one important feature is that the study's design needs to be done in such a way that the possibility of alternative causes for a difference between groups needs to be as low as possible. In the case of an intervention study, this is done by making the control and intervention group as similar as possible, both in patient characteristics and group characteristics in case of a clustered design, so that any difference observed during a trial can only be due to the intervention itself (198, 199).

One of the main reasons for systematic error, and low internal validity, is selection and information bias (200). Selection bias is defined as the selection of patients in such a way that group allocation is not random. An example of this would be that some patients who are deemed sicker than others, and thereby possessing a greater potential for improvement, are consciously, sub-consciously or randomly being allocated to the intervention group, thereby falsely increasing the treatment-effect (198, 200). Information bias is defined as a systematical measurement error, which occurs either due to an inaccurate outcome measure, or errors in data collection or data management. This is also often the source for reduced internal validity in cRCT. A systematic review was done by Eldrige et al. (2008) who investigated how well cRCT in primary care account for aspects related to internal validity (199). They found that what most often limits internal validity in cRCT is a lack of blinding of individual participants and that the persons assessing the primary outcome is not blind to group allocation (199). In the Pain-BPSD trial, this was considered, as both individual patients and the persons performing outcome assessments were blind for group allocation. However, despite best attempts to avoid knowledge on group allocation, information regarding the pharmacological management of patients is

available to all care-workers at the unit, making it impossible to achieve complete blinding for study-allocation.

There was an attempt to reduce selection bias by recruiting NH units, rather than individual patients, and ensuring no information regarding their medical situation was known prior to recruitments of units to the study. The possibility of selection bias was also reduced through randomization using a list of random numbers, making the likelihood of being randomized to both control and intervention equal for every NH-unit, ensuring an equal distribution of patients (198). As the baseline characteristics show, the control (86.5 years) and intervention group (84.9 years) only significantly differed according to age, highlighting an equal distribution of characteristics between groups. The downside of a clustered design is that any treatment effect observed at the individual level should be interpreted in light of the clustered design (201). There is a possibility that an outcome measure at the individual level can reflect a change at the clustered level, rather than a real change at the individual level (201). E.g. if a NH unit increased the amount of activities for residents to participate in, it is a possible that an individual resident would be registered as participating in an increased amount activities, even if he/she did not do so. Therefore, careful considerations must be made to adjust for this possibility. In the Pain-BPSD trial, clusters were defined as each individual NH unit, with its own staff only working at one unit. There is a possibility that an observed effect on NPS could be due to treatment practice at the individual unit, rather than a true effect on individual patients. However, the intracluster correlation coefficient in the Pain-BPSD study was estimated to 0.13, which could indicate that data for individuals within clusters were not highly dependent of which cluster they belonged (177). The intervention was aimed at each individual patient rather than the NH staff themselves, which contributes to reducing the likelihood of any intervention effect being due to cluster-effect rather than an effect on individual patients.

The main limitation of the methods used in paper 1 lies in the fact that the results are based on secondary analyses. The problem with this approach is that the power

calculations made for the Pain-BPSD trial were based on improvement on the CMAI total score, and not psychosis symptoms assessed by the NPI-NH (177). This increases the likelihood for random errors, meaning that any differences observed were due to chance, rather than a true difference (198). Secondary analyses increases the likelihood of both type I and type II errors (202). A type I error is rejecting the null-hypothesis of no difference when it is true, while a type II error being accepting the null-hypothesis, when it is not true (202). The likelihood of a type I error increases due to multiple testing of outcomes different than those the study was powered for. The likelihood of a type II error increases as the Pain-BPSD study was powered according to the change in CMAI total-score, hence the number of patients included in the study is based on this. This increases the risk of a type II error as there is a possibility that too few patients are included to detect a significant change in NPI-NH scores for the psychosis symptoms. The possibility of an adjustment for multiple testing exists, lowering the p-value from 0.05, thereby reducing the likelihood for a type I error, at the cost of increasing the likelihood for not rejecting a false null-hypothesis (202). This was, however, not done in paper 1, and the significance level was set at 0.05, which needs to be taken into consideration when interpreting the results, as they are less robust for random errors. It is also important to consider that the adjustment of the significance level for secondary analyses is not always needed as long as the results are interpreted precisely. (203)

External Validity

The external validity of a study is defined according to what degree the results from a study are generalizable for a broader population, which can be viewed as the entire NH population (198). The study includes PwD and significant behavioral disturbances, and excludes patients with severe renal or hepatic failure and a life expectancy <6 months, as well as patients with severe neurological or psychiatric disease. These criteria reduce the external validity of the study, in that it narrows the population to which the results apply. However, despite dementia and significant behavioral disturbances being a criterion, >80% of NH patients have dementia, while NPS are highly prevalent in NHs, meaning that the external validity is, to a certain

degree, maintained (4, 204). The study population of 18 NHs from 5 municipalities in Western Norway can be viewed like the rest of the Norwegian NH population, as it includes both urban and rural municipalities, increasing the external validity to the Norwegian NH population, and the Nordic NH population which can be viewed as fairly similar. The generalizability for NH populations in other countries are more uncertain. Recent data also suggest that European NH populations are more similar than previously thought, highlighting that the results may be generalizable to a European setting as well (205).

6.2.2 Paper 2

Study design

Cross-sectional studies are viewed as ideal for descriptive studies, and as a useful tool for generating hypothesis for further research. Therefore, it was viewed as a good starting point for further research into psychosis symptoms in NH patients (206). However, any conclusion regarding causality is not possible to do using this design, which is a drawback when investigating possible underlying factors for psychosis symptoms. To draw more certain conclusions regarding underlying factors, a prospective cohort study, with data collection for possible confounders, could be deemed as a more appropriate study design. The COSMOS-trial gathers data from a large and broad NH population and has data on possible confounders, such as medication use, which increases the reliability of the findings. A limitation lies in that the COSMOS-trial was designed with the primary aim of improving QoL in NH patients, thus data on a few key elements of the nature psychosis symptoms were not collected. Examples of this includes the duration of the symptoms and whether they were acute or chronic in nature, as the NPI-NH only measures the frequency of symptoms for the last week.

Internal Validity

The COSMOS-trial included NH units from both urban and rural municipalities, as well as large and small NH units from both the western and eastern part of Norway, this was arguably a representable group of the NH population of South Norway (16).

Ideally, units from a larger part of Norway could have been included to increase the internal validity, as this would have increased the number of patients with psychosis symptoms. The COSMOS-trial is a large study, which included 545 patients, but of them, only 112 patients had one or more psychosis symptoms. If a larger population were included, this would reduce the likelihood for a type II error when investigating potential underlying factors for psychosis symptoms (202). This is especially true for hallucinations, where only 45 patients of 545 (8.8%) experienced clinically significant symptoms. When interpreting the results from this paper, it is important to consider the use of measurement tools, such as the NPI-NH used to measure psychosis symptoms, and the MOBID-2 for pain assessment. Both measurement tools rely on a proxy-rater, which is fairly common in a NH setting, as the number of people with moderate to severe dementia are high, making proxy-rater evaluation necessary (123). In order to standardize measurements, the tools were therefore used for both NH patients with and without dementia.

When choosing measurement instruments for health-related outcomes, we have to consider if they are thoroughly tested for psychometric properties, and that they hold a high standard in the setting applied. A set of criteria for evaluating the quality of measurement tools has previously been developed by an expert panel, called the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) (207). The COSMIN-criteria were developed through a Delphi-process where the taxonomy of measurement properties relevant for instruments measuring health-related properties were decided (207). The process identified three domains for which instruments should achieve high standards: validity, which is defined as to which degree the instrument measures what it is supposed to measure (e.g. NPS for the NPI-NH); reliability, which is defined as to what degree an instrument is free from measurement error; and responsiveness, to what degree the instrument can detect change over time in the property which the instrument measures (207). This work resulted in the COSMIN-checklist, meant to aid in the evaluation of potential measurement instruments utilized in clinical studies (208). The tools used in the COSMOS-trial do all fulfill the requirements of the

COSMIN-checklist (1). This improves the internal validity of the measurements made in both papers 2 and 3, as the risk of any differences being observed being due to chance is lowered.

The use of an item score ≥4 to define a clinically significant symptom is general practice when using the NPI-NH (4, 59, 191). The use of a clinically significant symptom (item score ≥4), rather than the presence of any symptom on the NPI-NH (item score ≥1), can be discussed, as this will exclude patients with item scores 1-3 on the NPI-NH. However, the strength of this approach is that it will only include patients experiencing symptoms at least once a week, rather than patients experiencing symptoms less frequent than this. This is due to the generation of a FxS score (Frequency: 0-4, Severity: 1-3), where patients will need to have a score of at least 2 (experiencing symptom at least once a week) or more on the frequency score to achieve a FxS score ≥4. As NPS can have multiple causes, and the NPI-NH only records whether or not the symptom is present, thus a cut-off of ≥4 will make sure that only patients with a more persistent problem of NPS will be included.

As in paper 1, the use of secondary analyses is also a limitation for paper 2, as this increases the likelihood of random error, as calculation of statistical power for the COSMOS-trial was done according to QoL (202, 209). However, no correction for multiple testing is made, and most differences and associations found in paper 2 have a p-value below 0.01, which reduces the likelihood for a type I error. The lack of correction for multiple testing needs to be taken into consideration when interpreting the findings, especially p-values close to the significance level of 0.05.

External Validity

The COSMOS-trial uses broad inclusion criteria, and thereby includes what can be viewed as a normal NH population by Norwegian standards, which increases the external validity for countries with similar NH practice. While proxy-rating is a good option considering the nature of the NH population, it can never be viewed as a fully objective measure. An example of this was found by Blytt et al. (2017) who found a

large discrepancy between the sleep disturbance-item on the NPI-NH and the use of a more objective measure, the Actigraphy, which measures movement in patients at night (210). It is important to remember that symptoms assessed by a tool relying on observations by proxy-raters who do not observe that patient continuously may differ from the patient's own experiences. The use of proxy-rating will always reduce the validity of findings, but as the assessments are made by nurses or care-workers who know the patient well and observe them on a regular basis, this will reduce the difference between an objective measure and proxy-rating.

6.2.3 Paper 3

Study design

The results from paper 3 are based on two different study designs. The effect of the COSMOS-intervention on pain and psychosis symptoms is investigated through a cRCT, while the relationship between pain and psychosis symptoms is investigated by a prospective cohort design. The use of a prospective cohort design is, as previously discussed, better suited for investigating associations than a cross-sectional design, and one of the great strengths of paper 3 is that it is, to our knowledge, the first paper investigating the relationship between pain and psychosis symptoms through a longitudinal design. Some of the pros and cons of a cRCT have been discussed under a study design for paper 1; however, an additional element in the design of the COSMOS-trial that needs to be discussed is the use of a complex intervention.

A complex intervention is defined as an intervention that contains several interacting components put together to form an intervention (211). However, the numbers of behaviors targeted, and the expertise required by those delivering the intervention also increases the complexity of the intervention (212). The COSMOS-trial was developed according to guidelines for complex interventions and included elements, which have all previously been shown to have a positive impact on NH patients (86, 177, 181, 211, 213, 214). The interpretation of results from a complex intervention trial is complicated, as we need to consider to which degree the intervention has been

implemented in the target population and determine which elements of the intervention have impacted the outcome measure investigated in each study (211, 215).

Internal validity

NH units were randomized as a group to ensure that there were no cross-over of staff between control and intervention units. However, it is important to note that even if there were no cross-over of care-workers and nurses, this was not the case for physicians. This meant that some of the NH physicians (6 out of 36) worked at both control and intervention units, which meant that there was a risk that the COSMOS-intervention would bleed over to the control units. This is especially important to keep in mind when interpreting the results regarding pain, as the person who is ultimately responsible for choosing an appropriate pain treatment for NH patients is the NH physician. As some of the physicians worked at both control and intervention units, it is reasonable to expect that the knowledge they gained through the COSMOS-intervention could applied to patients in the control group, thereby reducing internal validity, and the possibility of finding an intervention-effect.
The COSMOS-trial was an intervention-study with the aim of implementing a multicomponent intervention in a NH-setting. To assess the internal validity of any findings from the trial, there is a need to assess how successfully the intervention has been implemented in the participating NH units. For the last 25 years, there has been an increasing focus on implementation science, and different frameworks have been developed to aid in evaluating how well an intervention has been implemented (216, 217). Two of the most widely used frameworks are the Proctor's framework and the Reach-Effectiveness Adoption, Implementation, and Maintenance (RE-AIM) framework (216-219).

As the COSMOS-trial is a multicomponent cRCT that includes a psychosocial intervention, it was important to investigate the keys factors for successful implementation observed in previous psychosocial interventions in dementia care to ensure the best possible implementation of the COSMOS-intervention. When

evaluating how well the COSMOS-trial was implemented, it is interesting to look at a systematic review Boersma et al. published in 2015, where they used the RE-AIM framework to investigate how well previous psychosocial interventions were implemented in their respective study populations (219). They found that one of the key factors for successful implementation was to use multiple implementation strategies, not just education (219). In the COSMOS-trial, all the participation of NHs, in addition to an education seminar, received regular follow-up from study-personnel, as well as written material with suggestions on how to ensure implementation of the COSMOS-intervention. This strategy could have increased the probability of a successful implementation as it did not only rely on education in itself to implement the intervention.

In the RE-AIM framework, reach is defined as the amount of the target population who participated in the intervention. In the COSMOS-trial, reach can be viewed as close to 100%, as all the NH units in the intervention group participated with at least 2 personnel in the education seminar. This ensured that all the NH units received the intervention (219). Proctor's framework defines acceptability as an important factor for implementation, which is defined as how satisfied the participants in the study are with the intervention (217). This was more difficult to assess in the COSMOS-trial, because this was not measured in the participating NH units. Meanwhile, the systematic feedback collected from the participating nurses concerning the intervention was positive regarding the importance of the knowledge being provided to the intervention units. The importance of the intervention being perceived as something useful is highlighted by Proctor et al. which states that the participants must feel that what they are doing are important based on their own and their colleague's experience (217).

Both Proctor's and the RE-AIM framework highlight the importance of adoption, being defined as the number of participants who used the intervention (217, 219). As all NH units were provided with patient logs for each patient, where they could register all procedures, such as medication review, pain assessment and activity

organization related to the COSMOS-intervention, this was a way of measuring the level of adoption. The logs could also be used to evaluate the implementation phase as this includes the amount of delivery of the intervention. As approximately 90% of the logs were partially or fully filled out, adoption could be viewed as relatively high (16, 187, 188). Though they were not filled out for all parts of the intervention, which makes it difficult to assess the level of implementation for all parts of the intervention.

Finally, maintenance, or sustainability is viewed as an important factor, which refers to what the degree the knowledge implemented by the COSMOS-intervention was maintained in the target population (217, 219). The midway-evaluation, as well as regular phone-contact with the COSMOS-ambassadors, and all the educational material received by the NH units, were important to ensure that knowledge was maintained. This guaranteed that each NH unit had the possibility of receiving help throughout the intervention phase to implement the intervention properly, either through feedback from research assistants or care-workers from the other NH units in the intervention group. However, a problem with this approach was that the intervention was delivered slightly differently in the NH units, as adjustments could be made along the way. Ideally, this could have been done in a more standardized way to increase the internal validity of the various findings from the study.

External validity

The external validity of the COSMOS-trial in general can be viewed as good, due to the broad nature of the NH population included. However, the findings on the intervention effect concerning both pain and psychosis symptoms must be viewed in the light of the complex nature of the intervention, as well as the variability in implementation of the different elements. It is not possible to view the effect of one part of the intervention without considering the effect of the other parts. As procedures regarding both ACP and the organization of activities varies considerably from NH to NH and country to country, this will reduce the external validity. However, the procedures and guidelines regarding pain assessment and treatment,

and medication review, varies to a lesser extent, which thereby balances some of the loss of external validity from the other components. The intervention does not include elements that is not already recommended in guidelines for Norwegian NHs (e.g frequent medication reviews and pain assessments), thereby highlighting that the intervention was done in a real-world clinical setting, and not in a strictly structured environment. The external validity of the association analyses can be viewed as very good, as these were based on observational data from a large heterogenous NH population, using measurement tools also used internationally.

6.3 Discussion of the results

The following section will first provide a short summary of the main finding, followed by a discussion of the results from all three papers, and compare them to existing research. In paper 1, no baseline association between pain intensity and psychosis symptoms were found, in contrast to paper 2, where a cross-sectional association between pain and psychosis symptoms were found in a more heterogenous NH population. Results from paper 3 showed that the association between pain and psychosis symptoms persisted over time, even when adjusting for potential confounders. In paper 2, it was found that patients with psychosis symptoms at baseline had lower QoL, lower ADL functioning, lower cognitive functioning, and used more regular medications.

In paper 1, results showed that a systematic assessment and treatment of pain reduced agitation and psychosis symptoms in PwD who were experiencing significant behavioral disturbances. However, the effect on psychosis symptoms were only seen for patients experiencing one or more psychosis symptoms at baseline. In paper 3, the efficacy of a multicomponent complex intervention on psychosis symptoms and pain were investigated, but no significant intervention effect was observed for psychosis symptoms, analgesic prescription or pain, except for a positive effect on musculoskeletal pain in PwD.

Relationship between pain and psychosis symptoms

The results from papers 1, 2 and 3 differ in that the two latter papers found an association between pain and psychosis symptoms as a group, and delusion individually, while the first did not. A difference in methodology and population could in part explain some of this difference. While paper 1 investigated the association between pain intensity and psychosis symptoms, papers 2 and 3 dichotomized pain into clinically significant pain (MOBID-2 ≥3) and no/non-significant pain and used this as a variable when investigating the association between pain and psychosis symptoms. This can perhaps indicate that the presence of pain plays a larger role than the intensity of pain. The two populations also differed in patient characteristics (Figures 1 and 2). While the Pain-BPSD population included NH patients with dementia and significant behavioral disturbances, the COSMOS-trial included virtually all NH patients both with and without dementia, except for terminal patients. The difference in population can be seen in that the prevalence of psychosis symptoms is significantly higher in the Pain-BPSD study (Delusion: 32.7% and Hallucinations: 17.3%) than in the COSMOS-trial (Delusion: 18.2% and Hallucinations: 8.8%). Pain scores were also higher in the Pain-BPSD study where the mean MOBID-2 score in the total population was 3.7 compared to 2.5 in the COSMOS-trial.

However, while more patients experienced psychosis symptoms in the Pain-BPSD trial, the more selective population could have made it more difficult to discover an association. The strength of the association found in the COSMOS-trial is that it persists over time, and that they vary together, meaning that when pain decreases so do psychosis symptoms and vice versa. The findings regarding the association between the prevalence of pain and psychosis symptoms from the Pain-BPSD study were only cross-sectional; it was not investigated over time.

When comparing the findings from this thesis with other studies, the results differ according to which study you examine. Two of the previous studies by Cohen-Mansfield et al. and Kunik et al. did not find any association between psychosis

symptoms and pain (171, 172). However, both studies investigated home-dwelling people with dementia, which makes the results less comparable to the one found in this thesis. An association between pain and delusion, and between pain and hallucinations, have previously been found (80, 173). Tosato et al. found an association between pain and delusion, while Atee et al. found an association between pain and hallucination (80, 173). Remarkably, both studies were conducted in NHs, making them more comparable to the results in this thesis. It is also interesting to see that neither Tosato et al. nor Atee et al. found an association between delusion, hallucinations and pain, but only between one of the two pairs. Study results suggest a stronger association between pain and psychosis symptoms in NH patients compared to home-dwelling PwD. This may be reasonable considering the different degrees of cognitive impairment, as studies suggests that psychosis is more prevalent in patients with moderate to severe dementia (4, 59). Patients with moderate to severe dementia are also at greater risk for undertreatment of pain, thereby increasing the risk for pain being an underlying problem in NH patients with dementia (150).

Effect of pain treatment on psychosis symptoms

The Pain-BPSD study is only the second study that has investigated the effect of pharmacological pain treatment on psychosis symptoms. Van Dam et al. (2020) investigated the effect of paracetamol on NPS in the QPID-trial, after paper 1 in this thesis. This was a double-blind placebo-controlled cross-over intervention trial, randomizing Dutch NH patients with dementia to paracetamol or placebo treatment (180). Interestingly, the study did not find that pain treatment had any effect on delusions nor hallucinations (180). There are a few differences between the Pain-BPSD trial and the QPID-trial, which can explain the diverging results. First and foremost, the QPID-trial does not consider the presence of pain when assigning paracetamol as the only analgesic used, while the Pain-BPSD trial assesses the level of pain before deciding on the analgesic to be used. Second, the QPID-trial only includes PwD with a moderate to low QoL, and excludes people using any regular analgesic pre-treatment, thereby excluding patients with possible pain.

In the Pain-BPSD trial, it is important to keep in mind that patients in the intervention group had a higher score for psychosis symptoms than the control group at baseline. However, the difference was non-significant, but could perhaps provide the intervention group with a greater potential for improvement than the control group. An important observation, which points to a true intervention effect, lies in that the psychosis symptoms in the control group decreased during the first weeks of the intervention period, before they remained stable for the remainder of the study period. This was opposed to the intervention group, where symptoms decreased until week 8 and increased in the following wash-out period. The decrease in the control group is perhaps due to a Hawthorne effect, meaning that participation in a trial may facilitate an improvement in itself (220). A type of placebo effect is also possible as the NH staff observing the patient did not know the group allocation of the patients they were observing. Therefore, it is possible that they expected a reduction in pain and NPS believing that the patient received individual pain treatment according to a SPTP.

The effect of the COSMOS-trial on psychosis symptoms and pain

The COSMOS-trial had no significant effect on psychosis or total pain score. As the COSMOS-intervention included elements that had the potential to reduce both pain and psychosis symptoms, such as systematic assessment and treatment of pain, as well as personalized activities, we expected that the intervention would have a positive effect (86, 177). The COSMOS-trial was designed for improvement of QoL, while NPS and pain was a secondary outcome measure. It is in the nature of a complex intervention that the elements are meant to interact in order to improve their primary goal, thereby increasing the risk that the effect on secondary outcome measures will be lower than if each element of the complex intervention were tested individually (211). As most of the studies the COSMOS-intervention was based on targeted agitated behavior, and not psychosis symptoms, the effect on psychosis symptoms was uncertain prior to the study.

As the COSMOS-intervention was a complex intervention, including different elements, it is difficult to directly compare the effect on psychosis symptoms and pain

with previously conducted studies. However, other multicomponent studies have been done that target either pain or NPS, including psychosis symptoms (89-91, 156). Only one of these studies evaluated the effect on psychosis symptoms in NH patients, and this was the TIME-intervention study by Lichtwarck et al. (2018), who found a small positive effect on delusion from baseline to week 8 of the study (89). However, in contrast to the COSMOS-trial, the TIME-study only included PwD and used a psychosocial intervention where NPS was the primary outcome, thereby increasing the chance of finding an effect on psychosis symptoms. The study by Pieper et al. found a positive effect on agitation, as well as on observed pain in NH patients with dementia (91, 156). The study had developed a stepwise treatment protocol to treat challenging behavior in PwD, including analgesics prescription for suspected pain as a part of the intervention. The primary outcome of the study was agitation measured on CMAI, while pain was a secondary outcome measure (221). The study did not investigate the effect of the intervention on the psychosis symptom cluster but did find a reduction in the total score for all 12 symptoms combined in the NPI-NH (91).

When the results of Pieper et al. and Lichtwarck et al. are compared with the results from this thesis, it seems reasonable that one of the main reasons that no effect on psychosis symptoms was observed is the difference in study design. The COSMOS-intervention focused on QoL rather than NPS, and the components with the potential of reducing psychosis symptoms was only part of a larger intervention. It is important to note that analysis of the intervention effect on staff-distress for psychosis symptoms found a significant positive intervention-effect from baseline to month 4, indicating that the intervention could have had a positive effect on NH staff to better handle patients with psychosis symptoms in the NH units (16). Although no effect on total pain was seen, a significant positive effect was found on musculoskeletal pain in PwD, which also highlights that the COSMOS-intervention could have had a positive effect on pain. However, as no effect on total pain or the NPI-NH score for psychosis symptoms was observed, no certain conclusions can be drawn. There is also a potential for a Dunning-Kruger effect, as was observed for QoL in the main study, where the NH units that did not receive any education tended to rate themselves

better than the intervention-units (16, 222). The intervention-units provided feedback that they felt bad after the education seminar, as they realized that their patients had the potential to have a better everyday life than they were currently having. However, it is difficult to measure if the Dunning-Kruger effect was present, and how much it influenced the proxy-raters when assessing each individual patient.

The use of opioid analgesics

In paper 1, the association between the use of opioid analgesics and psychosis symptoms was investigated but no significant association was found. However, no conclusion can be drawn based on this result alone, as the cross-sectional design is not ideal for investigating this matter, and the association between the use of opioid analgesics and the likelihood of experiencing psychosis symptoms have previously been documented (174). In paper 3, the use of regular opioid analgesics in the NH population was found to be >30%, a number that increased throughout the study-period, unaffected by the COSMOS-intervention. However, this number does not distinguish between strong and weak opioids, which is important to keep in mind when interpreting the results; nevertheless, opioids have the potential to induce psychosis symptoms through side-effects (66).

The use of opioid analgesics also has other negative effects such as increased risk of falls and adverse events due to drug-interactions (165, 168, 223). The high number of patients using opioid analgesics found in this thesis is therefore alarming and warrants a thorough investigation in the years to come. However, it is not within the scope of this thesis to make any recommendations regarding appropriate pain treatment with opioid analgesics.

6.4 Ethical Considerations

As stated by the Helsinki-declaration, underrepresented groups should have access to participation in research that could benefit them. This is relevant for NH patients with and without dementia. It also states that special care should be provided when research includes vulnerable groups (224). The use of informed consent is the gold-

standard for all research. In order to be able to give an informed consent, the person providing the consent must be able to understand what participation in the trial means. This includes what the aim of the trial is, all procedures involved, and any potential risks and benefits to the person participating. If the person is unable to understand this, presumed consent can be given. A presumed consent through a patient's next of kin, or legal guardian, is based on what the patient would have wanted to do had they been able to make a decision themselves, is acceptable (224). In both the Pain-BPSD trial and the COSMOS-trial, all patients and their next of kin or legal guardian were provided with this information both written and verbally, and in cases where the NH resident was unable to understand the potential risks and benefits, they had the opportunity to give a presumed consent (1, 177).

In the Pain-BPSD trial, the risk involved was related to the use of analgesic medication. There was an attempt to reduce this risk to a minimum through strict inclusion and exclusion criteria. Decisions regarding patient's pain treatment in the intervention group was conducted by the multidisciplinary team including the NH physician and the patient's primary caregiver who knew the patient well, and all the medical and personal information that could influence the effect of the analgesic medication prescribed. Adverse effects were monitored closely, and the dosage was reduced, or the patient was withdrawn from the study if any adverse effects appeared. The patients were also able to withdraw their consent at any time point. Patients benefitted from the trial in that they received a thorough pain assessment and pain treatment according to protocol developed by a team of specialists in treating pain in older adults (149, 177).

The intervention in the COSMOS-trial posed little risk of harm to the patient in that it was mainly an education-based non-pharmacological intervention, which aimed to implement elements that have previously been shown to benefit NH patients (1). A potential exception lies in the medication review, where altering the patient's medication can cause unwanted effects, which puts stress on the patient. However, any advice provided by the research team was optional, and NH physicians could at

any time revert medications back to what they were before the medication review. Some assessments made affected the patients directly, such as the MMSE and the MOBID-2 Pain Scale, which warranted thorough information regarding the data-collection process. Since the COSMOS-intervention involved a 2-day education seminar on best practice in important elements in treatment of NH patients, in addition to access to educational material for NH staff, it was considered unethical to withhold this from the NHs in the control group. Therefore, they received the education and the educational material after the completion of the data-collection at month 9.

In 2018, after the completion of the COSMOS and Pain-BPSD trial, the European Union introduced the General Data Protection Regulation (GDPR) to ensure the privacy of individuals with regard to personal data obtained by others (researchers, companies, etc.) (225). As a part of this regulation, whenever personal data of a certain nature, such as information on a person's medical history, is obtained, a Data Protection Impact Assessment (DPIA) is required to ensure the privacy of the information obtained. As this regulation was introduced after the completion of the COSMOS and Pain-BPSD trial, this was not done for these studies. All persons included in the study were assigned an ID-number, and the identification of the individual persons included in the study was only possible through a file on a secure server requiring a password to access the data. All data was stored on a secure server, while the questionnaires in anonymized paper-form were securely locked away until all data were digitalized.

7. Conclusion

This thesis aimed to investigate how pain and psychosis symptoms are related in NH patients, and how pain treatment affected psychosis symptoms. The thesis also investigated the characteristics of NH patients with psychosis symptoms, and how a complex multicomponent intervention affected pain, pain management and psychosis in NH patients.

The presence of pain was found to be associated with psychosis symptoms, both as a group and individually, and both cross-sectionally and over time when adjusting for potential confounders such as dementia severity and the use of opioid analgesics (226, 227). Patients who used antipsychotic medication had an increased likelihood of experiencing pain. Hallucinations were found to be associated with pain cross-sectionally, but this association did not persist over time. Patients with psychosis symptoms were found to have a lower QoL than patients without psychosis, as well as lower cognitive functioning, lower ADL-functioning and being prescribed more regular drugs (226).

The effect of pain treatment was investigated in a cRCT, where the intervention consisted of pharmacological pain treatment according to a stepwise protocol for treating pain (SPTP). Pain treatment reduced psychosis symptoms as a group in NH patients with dementia, experiencing at least one clinically significant psychosis symptom at baseline. A complex multicomponent intervention including elements such as education on systematic assessment and treatment of pain did not significantly affect psychosis symptoms in NH patients. Total pain was not reduced in response to the intervention, but a significantly positive intervention effect was found on musculoskeletal pain in PwD.

The use of regular opioid analgesics was not found to be significantly associated with psychosis symptoms cross-sectionally. The number of patients in the COSMOS-trial at baseline using regular opioid analgesic was 31%, showing a potential increasing trend in opioid prescription in Norwegian NHs.

8. Clinical implications and future perspectives

The findings from this thesis support an association between pain and psychosis symptoms as a group, especially delusion. This is an important finding for the clinician, as this adds to the sparse knowledge base regarding psychosis symptoms in the elderly, and for NH residents in particular. The association between pain and psychosis symptoms is further supported by the ability of pain treatment to reduce psychosis symptoms. If pain is an underlying trigger for psychosis symptoms, then a thorough pain assessment is warranted when making treatment decisions on psychosis symptoms to rule out the possibility of untreated pain as a trigger for the psychosis symptoms.

The importance of managing psychosis symptoms is highlighted by the clinical characteristics of NH patients experiencing them. The findings from this thesis suggest that they have a lower QoL and have more depressive symptoms than NH patients who do not experience psychosis symptoms. As psychosis symptoms are often treated with antipsychotic medication, an important finding is that NH patients with psychosis who used antipsychotic medication had lower QoL compared to patients with psychosis who did not use them. This highlights the necessity to identify patients who may benefit from antipsychotic medication and the awareness that underlying pain may trigger psychosis symptoms.

Although the results from this thesis found no effect of a multicomponent non-pharmacological intervention on psychosis symptoms, other studies have found promising results concerning the effect of psychosocial interventions on NPS. The development on proper guidelines regarding treatment of psychosis symptoms in NH patients warrants further research, with a focus on both psychosocial intervention and underlying factors such as pain.

One of the limitations of this thesis lies in the fact that the nature of psychosis symptoms, and its duration (acute or chronic), were not recorded. In the future, the author of this thesis wishes to perform a large-scale study on psychosis symptoms in

NH patients, preferably with a prospective cohort design, where psychosis symptoms and potential underlying factors are measured in detail on a regular basis over a longer period. This would have the potential to properly investigate both potential underlying factors, the nature of psychosis symptoms, and how they affect the patients experiencing them. This could be done by not only assessing the prevalence of psychosis symptoms, but also by describing how the symptoms occurred, the type of symptoms patients experience, and how they affect them, their family, and care-workers. Such a study could provide an important foundation for not only further research, but also as something for clinicians to base their treatment decisions on.

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10. Appendices

10.1 Regulation of compulsory treatment

Laws that regulate the use of compulsory treatment in health care:

The Patient and User Right act: (4)

§4.1 *Health care can only be given with the patient's consent, unless there, by law, is a reason to provide health care without consent. The consent is only valid if the patient is provided necessary information concerning their state of health and the content of the health care.*

§4.3 *If the patient, due to physical or mental disturbances, dementia, or mental disability, is obviously unable to understand what a consent means, the ability to consent, partly or fully disappears.*

§4.6 *If a patient lacks the ability to consent, the person providing health care can make decisions regarding health care of mild intervening character, concerning duration and scope.*
Health care of severe intervening character can only be given if it is the patients interest, and it is likely that the patient would have consented to the health care provided. If possible, information concerning the patient's wishes, should be obtained from the patient's next of kin.
Health care cannot be provided if the patient resists the health care, unless there is a legal reason to do so.

§4A-2 *Examination and treatment of mental disorders against the patients will can only be done on the legal basis of the Mental Health act.*

§4A-3 *In order to provide health care that the patient resists, confidence-building measures have to be attempted, unless it is futile to do so.*
If the patient still resists, or if health care personnel with certainty can say that the patient will resist, health care can be provided against the patient's will if:
a) Not providing the health care can cause serious harm to the patient
b) The health care is deemed necessary
c) The scope of the health care can be compared to the need.
Even if the terms stated above is met, health care can only be provided if it is deemed as the best possible solution for the patient.

10.2 Neuropsychiatric Inventory- Nursing Home version (Norwegian)

Variabel	N/A	Ikke til stede	Hyppighet	Intensitet	H x I Belastning
Vrangforestillinger	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Hallusinasjoner	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Agitasjon/aggresjon	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Depresjon/dysfori	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Angst	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Oppstemthet/eufori	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Apati/likegyldighet	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Manglende hemning	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Irritabilitet/labilitet	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Avvikende motorisk atferd	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Søvn	x	0	1 2 3 4	1 2 3	1 2 3 4 5
Appetitt/spise-forstyrrelser	x	0	1 2 3 4	1 2 3	1 2 3 4 5
			Total:		Total:

10.3 The MOBID-2 Pain Scale (Norwegian version)

APPENDIKS

MOBID–2 smerteskala

MOBILISATION – **O**BSERVATION – **B**EHAVIOUR – **I**NTENSITY – **D**EMENTIA

Patientens navn: **Dato:** **Tid:** **Avdeling:**

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

Smerteatferd

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

Smertelyd	**Ansiktsuttrykk**	**Avvergereaksjon**
«Au!»	Grimaserer	Stivner
Stønner	Rynker pannen	Beskytter seg
Ynker seg	Strammer munnen	Skyver fra seg
Gisper	Lukker øynene	Endringer i pusten
Skriker		Krymper seg

Smerteintensitet

Basert på observert smerteatferd; tolk styrken av smerteintensitet og sett kryss på linjen 0–10

SETT GJERNE FLERE KRYSS I RUTEN(E) FOR DIN(E) OBSERVASJONER

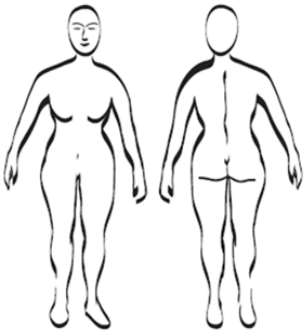
				0 er ingen smerte, 10 er verst tenkelig smerte
1. Led til å åpne begge hender	☐	☐	☐	0 1 2 3 4 5 6 7 8 9 10
2. Led til å strekke armene mot hodet	☐	☐	☐	0 1 2 3 4 5 6 7 8 9 10
3. Led til å bøye og strekke ankler, knær og hofteledd	☐	☐	☐	0 1 2 3 4 5 6 7 8 9 10
4. Led til å snu seg i sengen til begge sider	☐	☐	☐	0 1 2 3 4 5 6 7 8 9 10
5. Led til å sette seg opp på sengekanten	☐	☐	☐	0 1 2 3 4 5 6 7 8 9 10

APPENDIKS

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

Smerteatferd

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



Smerteintensitet

Basert på observert smerteatferd; tolk styrken av smerteintensitet og sett kryss på linjen 0–10

	0 er ingen smerte, 10 er verst tenkelig smerte
6. Hode, munn, hals	0 1 2 3 4 5 6 7 8 9 10
7. Bryst, lunge, hjerte	0 1 2 3 4 5 6 7 8 9 10
8. Mage – øvre del	0 1 2 3 4 5 6 7 8 9 10
9. Bekken, mage – nedre del	0 1 2 3 4 5 6 7 8 9 10
10. Hud, infeksjon, sår	0 1 2 3 4 5 6 7 8 9 10

Basert på alle observasjoner gi en helhetlig vurdering av pasientens smerteintensitet 0 1 2 3 4 5 6 7 8 9 10

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10.4 Paper 1

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Clinical Study

The Interactive Relationship between Pain, Psychosis, and Agitation in People with Dementia: Results from a Cluster-Randomised Clinical Trial

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Background. Neuropsychiatric symptoms are common in people with dementia, and pain is thought to be an important underlying factor. Pain has previously been associated with agitation, and pain treatment has been shown to ameliorate agitated behaviour. So far, the association between pain and psychosis and the effect of pain treatment on psychotic symptoms is unclear. Furthermore, the impact of opioid treatment on psychosis is not established. *Aim.* To investigate the efficacy of a stepwise protocol for treating pain (SPTP) on psychosis and agitation measured with the Neuropsychiatric Inventory, Nursing Home version, and to explore the impact of opioid analgesics on psychosis. *Method.* Secondary analyses are from a cluster-randomised controlled trial including 352 patients with advanced dementia and agitation from 18 nursing homes in Western Norway. The intervention group received pain treatment according to SPTP. *Results.* Pain was associated with disinhibition (adjusted OR: 1.21, 95% CI: 1.10–1.34) and irritability (adjusted OR: 1.10, 95% CI: 1.01–1.21) at baseline. Pain treatment reduced agitation ($p < 0.001$, df = 1; 300) and aberrant motor behaviour ($p = 0.017$, df = 1; 300). Psychosis was reduced in people with at least one symptom at baseline ($p = 0.034$, df = 1; 135). The use of opioid analgesics did not increase psychotic symptoms. *Study Registration.* This trial is registered with ClinicalTrials.gov (NCT01021696), Norwegian Medicines Agency, EudraCT (EudraCTnr: 2008-007490-20).

1. Introduction

Neuropsychiatric symptoms (NPS) are a feature in many neurodegenerative diseases, among other dementia, where over 90% of patients suffer from at least one NPS during the course of their disease [1]. NPS can be distressing for both patients and family alike and is often the main reason for admission to a nursing home (NH) [2]. NPS can be clustered in different ways. These clusters are most commonly defined by symptoms that present concurrently, like mood symptoms such as depression and anxiety, agitation symptoms such as aggression and irritability, and psychosis symptoms such as delusion and hallucination [3–6].

The aetiology of NPS is largely unknown, but factors like neuropathological changes in the brain, unmet psychosocial needs, and pain are thought to play a role [7]. Despite the multiple potential underlying factors, NPS are often treated with antipsychotic drugs with potential harmful side effects [8]. This highlights the importance of investigating the relationship between NPS and possible underlying treatable causes, such as pain, to avoid unnecessary antipsychotic drug use [9–11].

People in the later stages of dementia often reside in NHs and frequently experience pain, with 30–60% suffering daily from pain [12–14]. The cognitive decline with a subsequent loss of communicative abilities puts people with dementia at an increased risk of suffering from untreated pain [15, 16]. Research demonstrates that pain in people with dementia can act as a trigger for NPS such as agitation and mood symptoms [17, 18]. However, the relationship between pain

and psychosis symptoms is less well studied, and only an association between pain and delusion has previously been described. Tosato et al. investigated the association between pain and NPS in NH patients with cognitive impairment and found pain to be associated with delusion [19]. In contrast, Cohen-Mansfield et al. found no association between pain and psychosis symptoms in an adult day care population (≥60 years old) residing in the community [20].

Our own research demonstrated the efficacy of individual pain treatment on behavioural disturbances in NH patients with advanced dementia and found that pain treatment ameliorated agitation as assessed by the Cohen-Mansfield Agitation Inventory (CMAI) [9]. Secondary analyses showed that pain treatment also reduced verbal aggression and restlessness [10]. Mood symptoms such as depression, sleep and appetite disturbances, measured with the Neuropsychiatric Inventory, Nursing Home version (NPI-NH) [11], and pain intensity assessed by the Mobilisation Observation Behaviour Intensity Dementia-2 (MOBID-2) Pain Scale [13] were also found to be reduced. The effect of pain treatment on psychosis and agitation symptoms measured by NPI-NH has, however, not yet been investigated.

Although there are no official guidelines for pain treatment in people with dementia, the use of opioid analgesics in pain treatment is recommended in guidelines for older people [21–23]. However, some physicians can be reluctant to prescribe these drugs, often due to the fear of possible side effects such as delirium, which also includes psychotic symptoms such as hallucination and delusion [24, 25]. The association between opioid analgesics and psychosis can therefore give relevant information regarding delirium as a potential side effect of opioid drug use.

The primary aim of this study was to investigate the efficacy of pain treatment on psychosis and agitation and the association between pain, psychosis, and agitation in people with advanced dementia. In addition, we investigated whether the use of opioid analgesics increased the prevalence of delusion and hallucination in people with dementia. We hypothesized an association between pain and agitation at baseline, but not between pain and psychosis, and suggested that pain treatment will reduce symptoms of agitation, but not symptoms of psychosis. We also hypothesized that the use of opioid analgesics does not increase the prevalence of hallucination and delusion.

2. Method

We conducted secondary analyses from a cluster-randomised controlled trial (RCT), investigating the efficacy of treating pain on behavioural disturbances in NH patients with advanced dementia from 18 NHs in Western Norway. For a more detailed description of the study procedure, we refer to previous publications [9, 11, 13]. In brief, patients included in this study had moderate to severe dementia as defined by the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV); Functional Assessment Staging Test (FAST) score ≥ 4 [26]; Minimental State Examination (MMSE) score ≤ 20 [27], and clinically relevant behavioural disturbances as defined by a score ≥ 39 on CMAI [28]. Patients were excluded if they had an advanced medical disorder with expected survival ≤ 6 months, severe psychiatric or neurological disorder, hepatic or renal failure, a score ≥ 8 on the aggression item of the NPI-NH, with aggression as the predominant symptom [29], or allergy to paracetamol, morphine, buprenorphine, or pregabalin.

2.1. Study Design. Each NH unit was defined as a single cluster and was randomised to either intervention or control. Randomisation was performed by a statistician using Stata version 8, by generating a list of random numbers used for allocating each cluster to either intervention or control. The intervention group received individual pain treatment according to a stepwise protocol for treating pain (SPTP) for 8 weeks, followed by a 4-week washout period where analgesics were reverted back to preintervention treatment. The control group received treatment as usual. The SPTP was based on recommendations made by the American Geriatrics Society [22]. According to assessment of current medication and degree of pain, the patient was allocated to one of four steps, receiving either paracetamol (Paracetamol®), extended release morphine (Dolcontin®), buprenorphine transdermal patch (Norspan®) for patients with swallowing difficulties, or pregabalin (Lyrica®) for patients with suggested neuropathic pain. Physicians were instructed to keep the prescription unchanged if possible. Use of as-needed analgesics was not prohibited and was monitored during the study.

2.2. Outcome Measures. The primary outcome measure was NPS as measured by the NPI-NH [29]. The NPI-NH rates the frequency (F) and severity (S) of twelve different NPS. Frequency is rated on a scale from 1 to 4, where 1 represents occasionally (less than once a week) and 4 represents very frequent (daily or more often). Severity is measured on a scale from 1 to 3, where 1 represents mild (causes little stress for the patient) and 3 represents severe (puts very much stress on the patient and cannot easily be diverted by caregivers). The frequency and severity scores are multiplied ($F \times S$) to give an item score for each NPS, where a score ≥ 4 was viewed as a clinically significant symptom [30].

The NPS measured by NPI-NH were clustered in three groups: agitation (aggression, disinhibition, irritability, and aberrant motor behaviour), psychosis (delusion, hallucination, and euphoria), and mood (depression, anxiety, apathy, and sleep and appetite disturbances), according to factor analyses by Cheng et al. [6].

Pain intensity was assessed by the MOBID-2 Pain Scale [31–33]. This is a nursing staff-administered pain tool, consisting of two parts. The first part assesses pain originating from the musculoskeletal system during five active guided movements. The second part assesses pain that might be related to internal organs, head, and skin based on the caregivers' observation during the last week. Taking all items into account, the caregiver rated the patients' pain on a Numerical Rating Scale (NRS) ranging from 0 to 10, where 0 represented no pain and 10 the worst pain imaginable. This tool has been

thoroughly tested for its psychometric properties and showed good validity, reliability, and responsiveness [32, 33].

All assessments were conducted at baseline and Weeks 2, 4, 8, and 12 by the primary caregivers who knew the patient best in collaboration with a specialised study nurse.

2.3. Statistics. Differences in baseline characteristics were explored using an independent sample t-test for normally distributed variables; a Chi-squared test was used for categorical variables, and a Mann-Whitney U test was used for nonparametric variables. Associations between pain, psychosis, and agitation at baseline were investigated by using crude and adjusted logistic regression. Each symptom of psychosis and agitation represented the dependent variable, while total pain intensity, assessed by MOBID-2, represented the explanatory variable. Associations were adjusted for age, gender, dementia severity (assessed by MMSE and FAST), and activities of daily living (ADL) function assessed by Barthels ADL index [34]. The changes in $F \times S$ score between the intervention and control groups from baseline to Week 8 were compared using the Mann-Whitney U test. The association between opioid analgesics and delusion and hallucination was evaluated at baseline and Week 8 using logistic regression. Associations were adjusted for age, gender, dementia severity (MMSE and FAST), ADL function (Barthels ADL index), and pain intensity (MOBID-2). Statistic calculations were performed using the Statistical Package for Social Sciences (SPSS) version 22.

3. Ethics

Informed consent was obtained from patients who were cognitively able to understand the possible risks and benefits of the study. Consent was, if possible, obtained in a meeting where next of kin was present as well. A presumed consent was obtained from next of kin, or a legal guardian, if the patient was not able to give an informed consent. All consents were obtained in accordance with local law, approved by the Regional Ethical Committee for Medical Ethics in Western Norway (REK-Vest 248.08), and authorised by the participating institutions' review board.

4. Results

Three hundred and fifty-two patients from 60 NH units were included. Units were randomised to either intervention or control, generating 177 patients in the control group and 175 patients in the intervention group. With the exception of age ($p = 0.022$), we found no differences between the two groups. Baseline characteristics are described in Table 1. During the intervention period, 13 patients in the control and 25 in the intervention group were excluded, with no significant differences between the two groups [9]. At baseline, 71 people in the control group (40%) and 83 people in the intervention group (47%) had one or more symptoms of psychosis, while 128 people in the control group (72%) and 137 people in the intervention group (78%) had one or more symptoms of agitation. The most prevalent symptom was irritability (48%), while the least prevalent one was euphoria (9%).

Table 1: Sample characteristics of patients at baseline.

	Control ($n = 177$)	Intervention ($n = 175$)	df	p
Age (SD)[a]	86.5 (6.7)	84.9 (7.0)	350	0.022
Women (%)[b]	131 (74.0)	131 (74.9)	1	0.856
FAST (SD)[c]	6.0 (0.7)	6.1 (0.7)	349	0.057
MMSE (SD)[c]	8.4 (6.7)	7.5 (6.5)	346	0.177
Barthels ADL total score (SD)[c]	8.6 (5.6)	7.9 (5.7)	339	0.216
CMAI total score (SD)[c]	56.2 (16.1)	56.5 (15.2)	349	0.487
MOBID-2 (SD)[c]	3.7 (2.5)	3.8 (2.7)	325	0.988
Medications (SD)[c]	3.6 (1.6)	3.4 (2.1)	318	0.146
Analgesics (%)[b]	122 (68.9)	117 (66.9)	1	0.404
Paracetamol (%)[b]	94 (53.1)	99 (56.6)	1	0.665
Opioids (%)[b]	51 (28.8)	43 (24.6)	1	0.292
NSAIDS (%)[b]	9 (5.1)	13 (7.4)	1	0.364
Psycholeptics (%)[b]	112 (63.3)	104 (59.4)	1	0.458
Antipsychotics (%)[b]	13 (7.3)	17 (9.7)	1	0.465
Anxiolytics (%)[b]	86 (48.6)	80 (45.7)	1	0.589
Psychosis symptoms (%)[b]	71 (20.2)	83 (23.6)	1	0.209
Delusion (%)[b]	49 (27.7)	66 (37.7)	1	0.056
Hallucination (%)[b]	29 (16.4)	32 (18.3)	1	0.690
Euphoria (%)[b]	15 (8.5)	16 (9.1)	1	0.864
Agitation symptoms (%)[b]	128 (36.4)	137 (38.9)	1	0.285
Agitation/aggression (%)[b]	74 (41.8)	85 (48.6)	1	0.253
Disinhibition (%)[b]	56 (31.6)	59 (33.7)	1	0.760
Irritability (%)[b]	84 (47.5)	85 (48.6)	1	0.956
Aberrant motor behaviour (%)[b]	57 (32.2)	65 (37.1)	1	0.388

[a]Independent-samples t-test.
[b]Pearson's Chi-squared test.
[c]Mann-Whitney U test.

Related to symptoms of psychosis, no associations were found between pain and symptoms of psychosis at baseline. During the intervention period, no reduction in the psychosis cluster ($p = 0.091$, df = 1; 300), delusion ($p = 0.052$, df = 1; 300), hallucination ($p = 0.832$, df = 1; 300), and euphoria ($p = 0.507$, 1; 300) was observed in response to individual pain treatment compared to the control group from baseline and to Week 8 (Table 2, Figures 1–3). However, for people with one or more symptoms of psychosis at baseline, a decrease was observed in the psychosis cluster ($p = 0.034$, df = 1; 135) and delusion ($p = 0.031$, df = 1; 135) in the intervention group compared with the control group (Table 3, Figure 7).

At baseline, the adjusted logistic regression analysis showed a positive association between disinhibition and level of pain (OR: 1.18, aOR: 1.21, 95% CI: 1.10–1.34, and $p < 0.001$) and between irritability and level of pain (OR: 1.11, aOR: 1.10, 95% CI: 1.01–1.21, and $p = 0.032$), adjusted for confounders. During the intervention period, a decrease in the agitation cluster ($p < 0.001$, df = 1; 301), agitation/aggression ($p = 0.001$, df = 1; 301), and aberrant motor behaviour ($p = 0.017$, df = 1; 301) was found in the treatment group compared to

TABLE 2: Efficacy of treating pain on psychosis and agitation.

	Baseline			8 weeks			
	Control ($n = 177$)	Intervention ($n = 175$)	p^a	Control ($n = 157$)	Intervention ($n = 146$)	p^a	p change^b
NPI total score	31.4 (21.4)	34.8 (21.9)	0.132	26.6 (20.1)	18.9 (17.5)	<0.001	<0.001
Psychosis cluster	4.8 (5.8)	6.1 (6.9)	0.087	3.7 (4.9)	3.9 (5.5)	0.682	0.091
Delusion	2.6 (3.8)	3.6 (4.3)	0.030	2.0 (3.1)	2.0 (3.2)	0.813	0.052
Hallucination	1.5 (2.9)	1.8 (3.2)	0.427	1.1 (2.3)	1.4 (2.7)	0.405	0.832
Euphoria	0.7 (2.0)	0.8 (2.2)	0.887	0.6 (1.9)	0.5 (1.8)	0.123	0.507
Agitation cluster	13.4 (10.9)	14.8 (10.9)	0.155	11.3 (10.9)	7.8 (8.3)	0.007	<0.001
Agitation/aggression	3.7 (3.9)	4.2 (4.3)	0.373	3.4 (3.8)	2.1 (3.1)	0.001	0.001
Disinhibition	3.0 (4.0)	2.9 (3.8)	0.922	2.6 (3.9)	1.7 (3.0)	0.061	0.293
Irritability	3.7 (3.7)	4.2 (4.1)	0.338	3.0 (3.4)	2.3 (3.1)	0.092	0.093
Abb. motor behaviour	3.0 (4.5)	3.5 (4.7)	0.328	2.4 (3.7)	1.7 (3.6)	0.052	0.017

[a]Calculated by analyzing the difference between the intervention group and control group at each measurement point using the Mann-Whitney U test.
[b]Calculated by analyzing the difference in change of NPI-NH score in the intervention group versus the control group from baseline to Week 8 using the Mann-Whitney U test.

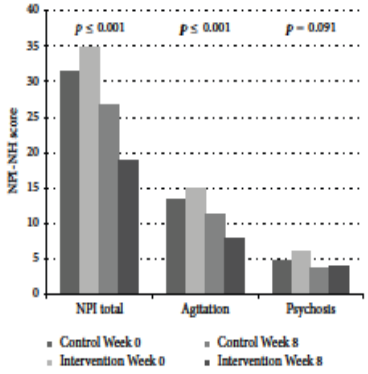

FIGURE 1: The efficacy of treating pain on psychosis and agitation.

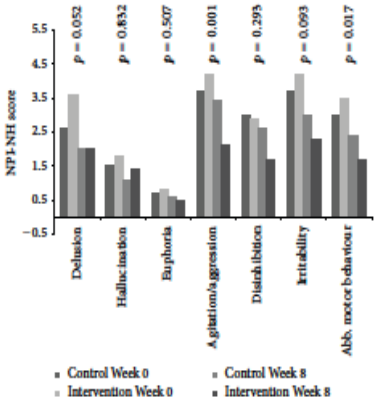

FIGURE 2: The efficacy of pain treatment on individual neuropsychiatric symptoms.

the control group (Table 2, Figures 1, 2, 4, 5, and 6). For people with one or more symptoms of agitation at baseline, a decrease during the intervention period was observed in the agitation cluster ($p < 0.001$, df = 1; 228), agitation/aggression ($p = 0.004$, df = 1; 228), and aberrant motor behaviour ($p = 0.007$, df = 1; 228) in the treatment group compared with the control group (Table 3, Figure 8).

At baseline, the use of opioid analgesics was not associated with the prevalence of delusions (OR: 0.97, aOR: 0.96, 95% CI: 0.56–1.65, and $p = 0.870$) or hallucination (OR: 0.76, aOR: 0.69, 95% CI: 0.34–1.41, and $p = 0.314$). Following the intervention period at Week 8, opioids were not associated with the prevalence of delusion (OR: 1.90, aOR: 1.89, 95% CI: 0.72–4.98, and $p = 0.200$) or hallucination (OR: 1.05, aOR: 1.26, 95% CI: 0.39–4.09, and $p = 0.700$).

5. Discussion

This study aimed to investigate the relationship between pain, psychosis, and agitation, the efficacy of treating pain on psychosis and agitation, and the potential impact of opioid analgesics on the development of hallucination and delusion in NH patients with advanced dementia.

The study showed that treatment of pain ameliorates the prevalence of psychosis and delusion in people with dementia who presented at least one psychosis symptom at baseline. It is also established that, in this study, opioid analgesics did not increase the prevalence of hallucination or delusion. These findings confirmed the hypothesis that pain is a potential underlying cause for psychosis and that proper pain management is needed in order to avoid psychotic symptoms. This provides important information for clinicians when pharmacological treatment options for pain are to be evaluated. Some clinicians can be reluctant to prescribe opioid analgesics for pain treatment of people with dementia, often due to fear of anticholinergic side effects, such as delirium [24]. Finally, we found that pain treatment

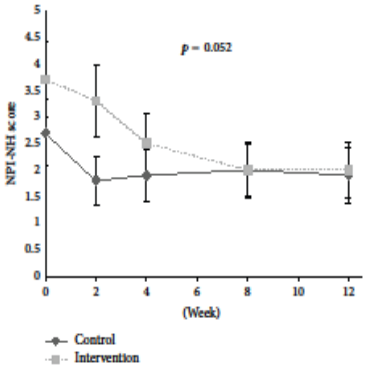

FIGURE 3: Development of delusion during the intervention and washout period.

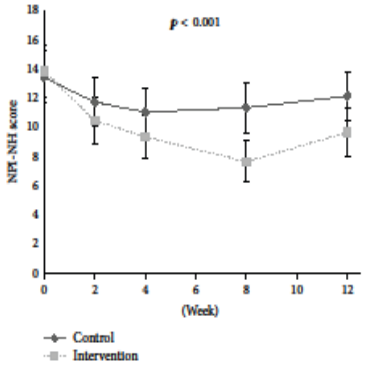

FIGURE 4: Development of agitation scores in clusters during intervention and washout period.

reduced agitation, aggression, and aberrant motor behaviour. This underlines previous findings where pain was found to be an important underlying cause for agitation assessed with CMAI in people with dementia. These findings highlight the fact that proper pain assessment should be a prerequisite when deciding treatment options for agitation in people with dementia.

The current study was the first parallel group-controlled trial investigating the efficacy of analgesics on psychotic symptoms in people with advanced dementia. Although individual pain treatment reduced psychosis in people with psychotic symptoms, pain was, interestingly, not cross-sectionally associated with hallucination and delusion at baseline. Tosato et al. used data from the Minimum Data Set (MDS) and investigated the relationship between pain

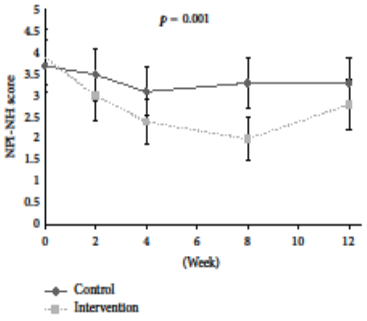

FIGURE 5: Development of agitation/aggression during the intervention and washout period.

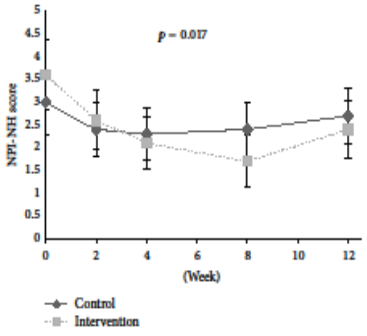

FIGURE 6: Development of aberrant motor behaviour during the intervention and washout period.

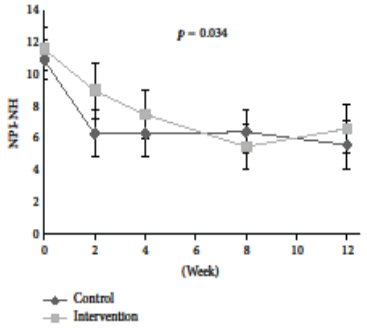

FIGURE 7: Development of the psychosis cluster in patients with one or more clinically significant NPS of psychosis at baseline (NPI-NH ≥ 4).

TABLE 3: Efficacy of treating pain on psychosis and agitation in patients presenting one or more clinically significant symptoms at baseline (NPI-NH ≥ 4).

	Baseline (SD)			8 weeks (SD)			
	Control ($n = 71$)	Intervention ($n = 83$)	p^a	Control ($n = 67$)	Intervention ($n = 70$)	p^a	p change^b
Psychosis cluster	10.5 (4.7)	11.6 (5.9)	0.314	6.4 (5.3)	5.6 (6.1)	0.148	0.034
Delusion	5.6 (4.2)	6.9 (4.0)	0.043	3.2 (3.7)	2.9 (3.6)	0.770	0.031
Hallucination	3.2 (3.8)	3.3 (4.0)	0.813	2.1 (3.1)	2.1 (3.3)	0.987	0.925
Euphoria	1.7 (2.9)	1.4 (3.1)	0.211	1.0 (2.2)	0.5 (1.9)	0.027	0.758
	Control ($n = 128$)	Intervention ($n = 137$)	p^a	Control ($n = 117$)	Intervention ($n = 113$)	p^a	p change^b
Agitation cluster	17.4 (9.7)	18.0 (9.6)	0.422	14.0 (11.0)	8.8 (8.8)	<0.001	<0.001
Agitation/aggression	4.7 (4.0)	5.1 (4.2)	0.441	4.2 (4.0)	2.5 (3.3)	0.001	0.004
Disinhibition	3.9 (4.3)	3.5 (4.0)	0.618	3.3 (4.2)	1.9 (3.2)	0.008	0.211
Irritability	4.8 (3.6)	5.1 (4.1)	0.664	3.6 (3.6)	2.6 (3.2)	0.023	0.183
Abb. motor behaviour	4.0 (4.7)	4.3 (4.9)	0.639	2.9 (3.9)	1.8 (3.5)	0.008	0.007

[a]Calculated by analyzing the difference between the intervention group and control group at each measurement point using the Mann-Whitney U test.
[b]Calculated by analyzing the difference in change of NPI-NH score in the intervention group versus the control group from baseline to Week 8 using the Mann-Whitney U test.

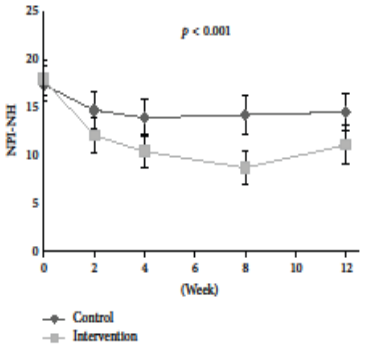

FIGURE 8: Development of the agitation cluster in patients with one or more clinically significant NPS of agitation at baseline (NPI-NH ≥ 4).

and psychiatric symptoms in 2822 NH residents with cognitive impairment and found an association between pain and delusion but not between pain and hallucination [19], contrary to our results. In Tosato's study, the interRAI MDS 2.0 instrument for long-term facilities was used to measure psychosis and pain, while our study used the MOBID-2 Pain Scale to measure pain. Cohen-Mansfield et al. also investigated the association between pain, delusion, and hallucination in an adult day care population and found no association between pain and delusion or pain and hallucination [20]. However, in contrast to our study, these people were not residing in NHs and patients suffering from dementia were not analyzed as a separate group. The study used the Behavioural Pathology in Alzheimer's disease rating scale to measure psychosis and a questionnaire, based on the short form of the McGill Pain Questionnaire, distributed to family and caregivers to measure pain. Pain should be measured by a tool thoroughly tested for psychometric properties, and among the measurement tools used, only MOBID-2 has been tested for validity, reliability, and responsiveness [32, 33].

We used a symptom clustering largely based on a factor analyses of the NPI-NH by Cheng et al., where the symptoms were clustered in three main groups: agitation, mood, and psychosis [6]. This clustering makes "clinical sense" and is in line with other previous studies. Hollingworth et al. grouped delusion and hallucination in a psychosis cluster, aggression and irritability in an agitation cluster, and disinhibition, euphoria, and aberrant motor behaviour in a behavioural dyscontrol cluster [3]. In a four-factor solution, Selbæk and Engedal grouped hallucination and delusion as a psychosis cluster and aggression, irritability, disinhibition, and aberrant motor behaviour in an agitation cluster [4]. Overall, the clusters may be viewed as merely theoretical constructs and changes assessed over time [4].

The reduction in psychosis was largely attributed to the reduction of delusion, as neither hallucination nor euphoria was reduced in response to pain treatment. This indicates that hallucination and euphoria may not be associated with pain. Traditionally, antipsychotics are recommended for short-time treatment of psychosis, also in people with dementia, despite potential harmful side effects and increased mortality [8]. Our results suggested that hallucination and euphoria were not associated with pain, making the use of antipsychotics in treatment of hallucination and euphoria more warranted than in treatment of delusion.

The use of opioid analgesics did not increase the prevalence of delusion or hallucination at baseline, or after the 8-week intervention. This is of key importance, because opioid analgesics such as morphine or buprenorphine can have multiple side effects such as confusion and delirium caused by anticholinergic activity [24]. Notably, delirium, psychosis, and depression have several similarities in people with dementia, making them difficult to distinguish and diagnose. This highlights the importance of trained staff in order to discriminate between the more acute state delirium and more chronic symptoms in dementia [25].

The reduction of agitation in response to pain treatment was fairly expected, as previous analyses on the study population have shown a decrease in behavioural disturbances, especially agitation, as measured using CMAI [9, 10]. NPI-NH does however measure more specific symptoms in contrast to CMAI, which measures more specific behavioural items. Therefore, the efficacy of pain treatment on the specific symptom aberrant motor behaviour is an interesting finding, supported by previous studies which found that pain treatment may reduce agitation. An article by Flo et al. reviewed studies on pain management in people with dementia and found that pharmacological pain treatment could reduce agitation [17]. Achterberg et al. reviewed the efficacy of pain management in people with dementia and found that pain can be a possible underlying cause for agitation and that a thorough pain assessment and management can ameliorate agitation [16]. The present analyses also found that there was an association between pain and disinhibition and irritability at baseline. While previous studies have found an association between pain and agitation, the direct association between pain, disinhibition, and irritability has not previously been described [17, 18, 35]. Our results showed that NPS associated with pain at baseline, like irritability and disinhibition, were not reduced in response to pain treatment. Results also showed that NPS not associated with pain at baseline, like agitation and delusion, were reduced in response to pain treatment. This paradox simply highlights the complex aetiology of NPS of agitation, and a thorough assessment of all possible underlying causes is important when deciding on possible treatment options for neuropsychiatric symptoms in people with dementia. Pain and behaviour are strongly intertwined, and the efficacy of both behavioural interventions and pain medication can improve both pain and behaviour [36].

Strengths and Limitations. This is the first RCT investigating the efficacy of treating pain on psychosis. Results came from secondary analyses from a previous study where CMAI was the primary outcome and NPI-NH was a secondary outcome. Inclusion criteria were therefore based on behavioural disturbances measured using CMAI. The number of study participants was also a limitation, as the group of patients with psychosis at baseline were a subgroup of the original population and a small sample. Despite this, the study is still the largest RCT investigating the efficacy of treating pain on psychosis and agitation.

6. Conclusion

Pain seems to be an underlying cause of psychosis and especially delusion. In addition, pain seems to be an underlying cause of agitation, such as aberrant motor behaviour. Thus, proper pain assessment is needed when treating these symptoms in people with dementia. The use of opioid analgesics does not seem to increase the prevalence of delusion and hallucination; therefore, the reluctance to use them may not necessarily be to the benefit of the patient.

Ethical Approval

The study was approved by the Regional Ethical Committee for Medical Research of Western Norway (248.08).

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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10.5 Paper 2

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RESEARCH ARTICLE

WILEY International Journal of Geriatric Psychiatry

Psychosis symptoms in nursing home residents with and without dementia—Cross-sectional analyses from the COSMOS study

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Objective: To investigate the characteristics of nursing home residents with psychosis and the association with potential underlying factors, such as pain, sleep disturbances, and antipsychotic medication.

Method: Five hundred forty-five residents with and without dementia from 67 Norwegian nursing home units were included in the cross-sectional analyses. Psychosis was the main outcome measure in our study; other outcome measures include quality of life (QoL), activities of daily living (ADL) function, cognitive function, pain, and antipsychotic medication.

Results: One hundred twelve residents had one or more symptoms of psychosis, and compared with residents without psychosis, they had lower QoL ($p < 0.001$), ADL function ($p = 0.003$), and cognitive functioning ($p = 0.001$). Adjusted logistic regression analyses showed that psychosis was associated with the prevalence of pain (OR: 3.19; 95% CI, 1.94-5.24), sleep disturbances (OR: 4.51; 95% CI, 2.91-6.99), and total number of medication (OR: 1.10; 95% CI, 1.03-1.17). Residents with psychosis but without antipsychotic medication had better QoL ($p = 0.005$) compared with residents receiving any antipsychotics.

Conclusion: Psychosis in NH residents is associated with pain, sleep disturbances, and number of medications. Residents with psychosis have poor QoL, although better QoL was observed among those who did not use antipsychotic medication.

KEYWORDS

dementia, neuropsychiatric symptoms, nursing home, pain, psychosis, psychotropic drugs, quality of life

1 | BACKGROUND

In an increasingly older population, more people are in need of institutional care, and in Norway, almost 50% of all deaths occurs in a nursing home (NH).[1] These individuals are characterized by complex care needs, multiple acute and chronic conditions, and over 80% have dementia.[2] Neuropsychiatric symptoms (NPS) such as agitation, psychosis, and depression are often related to dementia, and over 90% experience at least one such symptom during the course of the disease.[3,4] Symptoms of psychosis such as delusion and hallucinations are frequent, and the prevalence of delusion and hallucinations in an NH population varies between 14% to 33% and 5% to 27%, respectively.[2,5-7] Along with NPS, pain is frequent in NHs, and between 30% and 60% of residents experience pain on a daily basis.[8-10]

Psychosis symptoms can be distressing for residents, families, and carers alike, increases the risk of admission to a health care institution, and is associated with poor Quality of Life (QoL).[11-14] In older

residents, symptoms of psychosis have a multifactorial aetiology and are often a result of delirium or dementia.[15] In 2016, Helvik et al found that psychosis in NH residents was associated with poor activities of daily living (ADL) functioning and dementia severity.[3] In 2012, Tosato et al found an association between delusion and pain in a European NH population.[16] The association between psychosis and pain was further studied by Habiger et al, who found that symptoms of psychosis such as delusion were ameliorated in residents receiving pain treatment.[17]

Recent guidelines on the treatment of NPS in people with dementia recommend the use of non-pharmacological interventions as a first-line approach.[18,19] For psychosis symptoms that are not in an acute phase, these guidelines highlight the importance of identifying and treating possible underlying causes when deciding on treatment options for NPS.[18,19] However, the treatment of psychosis is complex, and the medication of choice for psychosis symptoms is often antipsychotics such as haloperidol and risperidone, which are also known for harmful side effects such as accelerated cognitive decline and cerebrovascular events, in this vulnerable population.[20-22] Psychotropic drugs in NHs are frequently prescribed, and in 2016, Gulla et al found that 73% of Norwegian NH residents used at least one psychotropic drug, but only 14% of the residents used antipsychotic medication.[23] Janus et al found that the antipsychotic prescription rate in Western European NHs ranges from 12% to as high as 59% in some countries.[24]

The aim of this study is to explore the characteristics of NH residents with psychosis and to investigate whether residents with psychosis using antipsychotic medication differ from those not using antipsychotic medication. We aim to investigate possible underlying factors associated with symptoms of psychosis and hypothesize that these symptoms are associated with poor QoL, cognitive function, and ADL function. We also hypothesize that there are few clinical differences between residents with psychosis with and without antipsychotic drug prescription.

2 | METHOD

This study is based on baseline data from the COSMOS study. COSMOS is an acronym and stands for COmmunication, Systematic assessment and treatment of pain, Medication review, Occupational therapy and Safety. The study protocol was published by Husebo et al in 2015 and is fully described elsewhere.[25]

The study was conducted from 2014 to 2015 and included 545 residents from 67 NH units, in both western and eastern Norway. The COSMOS study is a cluster randomized controlled trial (RCT), investigating the effect of the implementation of a complex intervention with focus on the four key COSMOS subjects lasting for 4 months and followed up at month 9. Inclusion criteria were NH residents 65 years old and above, with and without dementia. Residents with a life expectancy 6 months and below or residents with schizophrenia were excluded from the study. The data in this article are based on the baseline data collection.

Key points

- Symptoms of psychosis are common in a nursing home population.
- Nursing Home residents with symptoms of psychosis had lower Quality of Life, ADL, and cognitive function.
- Pain, sleep disturbances, and number of drugs prescribed were associated to psychosis and should be evaluated when making treatment decisions for symptoms of psychosis.

2.1 | Outcome measures

The primary measure for assessment of psychosis was the Neuropsychiatric Inventory Nursing Home version (NPI-NH), which was developed by Cummings et al,[26] translated into Norwegian and thoroughly tested for reliability and validity by Selbaek et al.[27] The NPI-NH assesses 12 different NPS such as delusion, hallucinations, depression, and sleep disturbances and assesses the frequency (F) and severity (S) of each symptom. Frequency is measured on a scale from 0 to 4, where 0 represents not present, and 4 represents symptom present on a daily basis. Severity is measured on a scale from 1 to 3, where 1 represents mild severity with little stress for the resident, and 3 represents a severe symptom with much stress on the resident. The frequency and severity score are then multiplied together to generate a total score for each symptom (FxS) ranging from 0 to 12. A resident was defined as having an NPS, when he had an FxS score greater than or equal to 4, as this is deemed a clinically significant score.[28] The different symptoms can be clustered together in various ways, and symptom clusters contain the NPS that are closely related in the clinical setting, such as depression and anxiety in a mood cluster, agitation and irritability in an agitation cluster, and delusion and hallucination in a psychosis cluster.[29-31] The psychosis cluster in our study includes both hallucinations and delusion, and residents were classified as having psychosis if they had an FxS score greater than or equal to 4 on either one or both of these symptoms. Sleep disturbances and appetite disturbances were assessed using their respective items on the NPI-NH.

For investigation of associations with psychosis, we included assessment tools for cognitive function, depression, QoL, behavioral disturbances, ADL function, and pain. Cognitive performance was assessed using the Mini Mental State Exam (MMSE) generating a score from 0 to 30, where a low score indicates poor cognitive function.[32] The category Activities of daily living was assessed using the Lawton and Brody's ADL assessment tool, generating a score from 0 to 30, where higher scores indicate lower functional independence.[33] Depression was assessed using the Cornell Scale for Depression in Dementia (CSDD) generating a score of 0 to 38, where a high score indicates a severe degree of depression.[34] QoL was assessed using the 18-item version of QoL in dementia (QUALIDEM) generating a score from 0 to 54 where a low score indicates poor QoL while a high

score indicates a high QoL.[35] QoL was also assessed using QoL in late stages of Dementia (QUALID), generating a score from 11 to 55 where a high score indicates poor QoL.[36] Behavioral disturbances were evaluated by the Cohen-Mansfield Agitation Inventory (CMAI) generating a score from 29 to 203, where a high score indicates a high level of behavioral disturbance.[37] Pain was evaluated by the Mobilisation-Observation-Behavioral-Intensity-2 Pain Scale (MOBID-2), which assesses pain related to the musculoskeletal system, internal organs, head, and skin and generates a score from 0 to 10, where 0 indicates no pain, and 10 indicates the highest pain possible.[38,39] Information about diagnoses and medication were obtained from the residents' medical records. Psychotropic drugs were defined as the group noted N05 in the Anatomical Therapeutic Chemical (ATC) register. Psychotropic drugs were also divided into the subgroups antipsychotics (N05A), anxiolytics (N05B), and hypnotics and sedatives (N05C) in line with ATC register. The MMSE were performed by one of four full-time researchers in the COSMOS team consisting of one physician, one nurse, and two medical students. All other assessments were performed by a caregiver who knew the resident well, after receiving training from the COSMOS team on using the different assessment tools.

2.2 | Statistics

To test differences in characteristics between residents with and without clinically significant psychosis symptoms, independent sample *t* test was used for normally distributed variables; a chi-squared test was used for categorical variables and Mann-Whitney U test for non-normally distributed variables. To test associations between symptoms of psychosis and other factors (ADL function, pain, depression, medication, QoL, nighttime disturbances, and appetite disturbances as measured with the NPI-NH), logistic regression with robust standard error estimation adjusting for clustered design was used. Odds ratios were calculated for each factor and adjusted for age, gender, dementia diagnosis, and cognitive functioning. Statistical analyses were performed using IBMs Statistical Package for Social Sciences (SPSS) version 23 and StataCorps Stata version 15.0.

2.3 | Ethics

Verbal and written informed consent was obtained from residents who were cognitively able to understand the information regarding the COSMOS study. In residents lacking the ability to consent, a verbal and written presumed consent was obtained, after explaining the study procedure, from the residents' next of kin or legal guardian, with the resident present if possible. The trial was approved by the Regional Committee for Medical and Health Research Ethics, West Norway (REK 2013/1765) and registered at clinicaltrials.gov (NCT02238652).

3 | RESULTS

Five hundred and forty-five residents from 67 NH units were included in the study; 33 residents had incomplete data for the NPI-NH assessment of psychosis symptoms, resulting in 512 participants in the final analyses. The mean age was 87 years, and 73% were women (Table 1). One hundred and twelve residents (21.9%) had one or more symptoms of psychosis, 94 (18.4%) had delusion, and 45 (8.8%) had hallucinations. Compared with residents without psychosis, those with psychosis more often had dementia (p = 0.004, df: 510), poorer QoL on both the QUALIDEM (p < 0.001, df: 502) and QUALID (p < 0.001, df: 502) assessment tool, more behavioral disturbances (p < 0.001, df: 493), and lower ADL function (p = 0.003, df: 505) (Table 1). Residents with psychosis also had higher depression scores assessed by CSDD (p < 0.001, df: 415), more sleep disturbances (X^2 = 47.7, p < 0.001), poorer cognitive function on the MMSE (p = 0.001, df: 472), and more pain (p = 0.002, df: 438) (Table 1). More psychotropic drugs were prescribed to residents with psychosis (p = 0.015, df = 503), without differences between antipsychotics, anxiolytics, and hypnotics and sedatives (Table 1 and Figure 1). Residents with psychosis using no antipsychotic medication had better QoL on the QUALIDEM (p = 0.005, df = 108) and lower total scores on the NPI-NH (p = 0.035, df = 108) compared with those treated with antipsychotic medication. Residents with psychosis using antipsychotic medication did not differ from residents using no antipsychotic medication in ADL function, pain, and cognitive function (Figure 2).

In the logistic regression analyses with adjustment for clustered design, age, sex, dementia diagnose, and cognitive function, psychosis was found to be associated with poor QoL (adjusted odds ratio: 0.89; 95% CI, 0.86-0.92; p < 0.001), depression (aOR: 1.21; 95% CI, 1.15-1.27; p < 0.001), number of prescribed drugs (aOR: 1.10; 95% CI, 1.03-1.17; p = 0.005), nighttime disturbances (aOR: 4.51; 95% CI, 2.91-6.99; p < 0.001), appetite disturbances (aOR: 3.46; 95% CI, 1.65-7.27; p = 0.001), and pain (aOR: 3.19; 95% CI, 1.94-5.24; p < 0.001) (Table 2). The same associations were found for the individual symptoms of delusion and hallucinations, with the exception of an association between hallucinations and ADL function (aOR: 1.19; 95% CI, 1.07-1.33; p = 0.773) (Table 2). Psychosis symptoms were found to be associated with all other NPS measured with the NPI (Table 2). The same associations were found for the individual symptom delusion, while hallucinations were found to not be associated with apathy (aOR: 2.02; 95% CI, 0.91-4.48; p = 0.082), disinhibition (aOR: 1.37; 95% CI, 0.56-3.31; p = 0.490), and euphoria (aOR: 1.40; 95% CI, 0.30-6.57; p = 0.668) respectively (Table 2).

4 | DISCUSSION

The study showed that NH residents with psychosis had poorer QoL compared with residents without psychosis and that residents with psychosis not using any antipsychotic medication had better QoL compared with residents not using antipsychotics. Psychosis was

TABLE 1 Characteristics of residents with and without psychosis

	Psychosis (n = 112)	Without Psychosis (n = 400)	p Value	Total Population (n = 512)
Women (%)	87 (77.7)	292 (73.0)	0.318[a]	379 (74.0)
Age (SD)	86.6 (7.5)	86.7 (7.4)	0.629[b]	86.9 (7.4)
Dementia diagnosis (%)	86 (76.8)	248 (62.0)	0.004[a]	334 (65.2)
MMSE score (SD)	9.0 (6.7)	11.8 (7.8)	0.001[c]	11.2 (7.7)
ADL score (SD)	18.5 (5.6)	16.8 (5.1)	0.003[c]	17.1 (5.3)
Cornell score (SD)	12.5 (7.2)	5.7 (5.0)	<0.001[c]	7.1 (6.2)
CMAI score (SD)	55.2 (18.7)	38.6 (11.8)	<0.001[c]	42.3 (15.3)
QUALID score (SD)	26.9 (8.3)	20.0 (6.5)	<0.001[c]	21.5 (7.5)
QALIDEM score (SD)	32.7 (8.8)	41.2 (8.1)	<0.001[b]	39.2 (8.9)
MOBID-2 score (SD)	3.2 (2.6)	2.3 (2.6)	0.002[c]	2.5 (2.6)
NPI-NH total score (SD)	40.1 (23.3)	11.6 (14.0)	<0.001[b]	17.8 (20.2)
NPI-NH total carer strain (SD)	15.4 (9.3)	4.8 (6.0)	<0.001[c]	7.0 (8.1)
Agitation/aggression (%)	57 (50.9)	61 (15.3)	<0.001[a]	118 (23.0)
Depression (%)	53 (47.3)	66 (16.5)	<0.001[a]	119 (23.2)
Anxiety (%)	50 (44.6)	67 (16.8)	<0.001[a]	117 (22.9)
Euphoria (%)	8 (7.1)	12 (3.0)	0.044[a]	20 (3.9)
Apathy (%)	26 (23.2)	47 (11.8)	0.002[a]	73 (14.3)
Disinhibition (%)	33 (29.5)	48 (12.0)	<0.001[a]	81 (15.8)
Irritability (%)	74 (66.0)	87 (21.8)	<0.001[a]	161 (31.4)
Aberrant motor behavior (%)	28 (25.0)	30 (7.5)	<0.001[a]	58 (11.3)
Appetite disturbances (%)	20 (17.9)	25 (6.3)	<0.001[a]	45 (8.8)
Sleep disturbances (%)	46 (41.0)	61 (15.3)	<0.001[a]	107 (20.9)
Drugs as prescribed (SD)	8.4 (3.7)	7.9 (3.8)	0.226[c]	8.0 (3.8)
Psychotropics (%)[d]	66 (58.9)	185 (46.3)	0.015[a]	251 (49.0)
Antipsychotics (%)	20 (17.9)	57 (14.4)	0.333[a]	77 (15.0)
Anxiolytics (%)	28 (25.0)	79 (19.8)	0.216[a]	107 (20.9)
Hypnotic and sedatives (%)	41 (36.6)	115 (28.8)	0.101[a]	156 (30.5)
Analgesics (%)	74 (66.0)	227 (56.8)	0.064[a]	301 (58.8)
Antidepressants (%)	46 (41.1)	163 (40.8)	0.951[a]	209 (40.8)
Antidementia drugs (%)	24 (20.8)	55 (13.8)	0.047[a]	79 (15.4)
Anti-Parkinson drugs (%)	6 (5.4)	21 (5.3)	0.964[a]	27 (5.3)
Drugs as needed (SD)	4.0 (2.0)	3.2 (2.2)	<0.001[c]	3.4 (2.2)
Psychotropics (%)[d]	90 (80.4)	230 (57.5)	<0.001[a]	320 (62.5)
Antipsychotics (%)	8 (7.1)	21 (5.3)	0.444[a]	29 (5.7)
Anxiolytics (%)	73 (65.2)	172 (43.0)	<0.001[a]	245 (47.9)
Hypnotic and sedatives (%)	42 (37.5)	99 (24.8)	0.008[a]	141 (27.5)
Analgesics (%)	93 (83.0)	289 (72.3)	0.020[a]	382 (74.6)

Abbreviations: ADL, activities of daily living; CMAI, Cohen-Mansfield Agitation Inventory; MMSE, indicates Mini Mental State Exam; MOBID-2, Mobilization-Observation-Behavior-Intensity-Dementia-2 pain scale; QUALID, Quality of Life in late-stage Dementia; QUALIDEM, Quality of Life in Dementia; NPI-NH, Neuropsychiatric Inventory Nursing Home version.

[a]Chi-squared test.

[b]Independent t-test samples.

[c]Mann-Whitney U test.

[d]Use of any Antipsychotic, Anxiolytic, and Hypnotic and Sedative.

found to be associated with pain, number of drugs prescribed, sleep disturbances, appetite disturbances, and depression. The findings are important for the clinician because they highlight the detrimental impact that symptoms of psychosis have on NH residents, the importance of treating the symptoms and possible underlying causes, and the complexity of such treatment.

Our study is one of the largest studies focusing on psychosis in NH residents and adds important knowledge about psychosis in NH residents. The findings regarding psychosis and QoL are in line with previous studies where psychosis was found to have a negative impact on QoL. Mjorud et al investigated variables associated with QoL in Norwegian NH residents with dementia and found an association

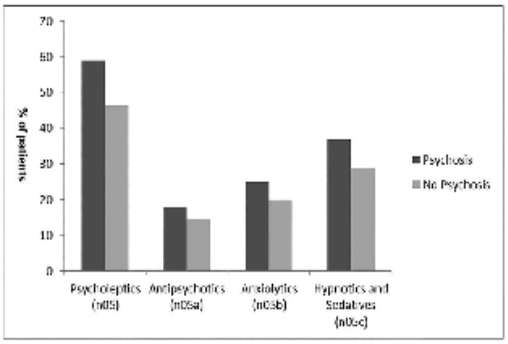

FIGURE 1 Psychotropic drug prescription in residents with and without psychosis

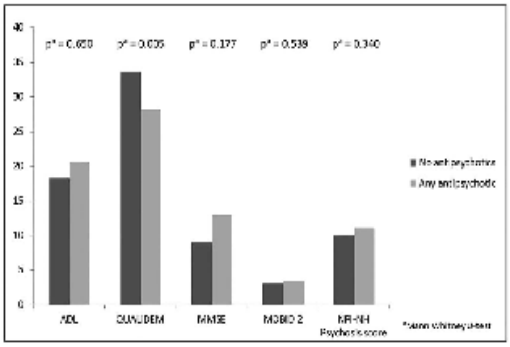

FIGURE 2 Residents with psychosis using antipsychotics compared with residents with psychosis using no antipsychotics

between poor QoL and psychosis,[34] while Wetzels et al studied determinants of QoL in Dutch NH residents with dementia and found that psychosis was associated to lower QoL.[13] As in our study, the NPI-NH was used to measure psychosis, making the studies comparable. The association between psychosis and sleep disturbances is an important finding. Previous studies on psychosis and sleep disturbances have found an association between psychosis and insomnias.[40,41] These studies, however, were only performed on patients aged 16 to 74 years, and there is a lack of studies on the association between psychosis and sleep disturbances in patients aged 75 years and older. Sleep disturbances in our study are also a more broad term as it includes all types of sleep disturbances not only insomnia. It is also important to note that a recent study by Blytt et al found a large discrepancy between the NPI-NH item sleep disturbances and objectively measured sleep disturbances with actigraphy.[42] Since our results are cross-sectional, we cannot claim causality, so there is a need for further studies, and the use of a more reliable measure of sleep disturbances may be warranted in the future.

A previous study by Helvik et al on the severity of NPS in 2898 Norwegian NH residents found an association between psychosis severity and ADL function.[3] Although residents with psychosis had lower ADL function than residents without psychosis in our study, no significant association was found between psychosis and ADL function when adjusting for confounding factors such as age and cognitive function. A reason for this difference could be that the two symptoms of psychosis impact ADL function in different ways. This is supported by our results, as hallucinations were found to be associated with poor ADL function when adjusting for confounding factors, while no such association was found for delusion. It is also worth noting that Helvik et al investigated the association between psychosis severity and ADL function and not between ADL function and the presence of psychosis as in our study.

The finding that NH residents with psychosis using any antipsychotic medication had poorer QoL when compared with residents with psychosis using no antipsychotics highlights a challenge in treating psychosis in NH residents. Antipsychotic medication may be

TABLE 2 Symptoms of psychosis and associated features

	OR (95% CI)	p Value[a]
Psychosis		
Pain (MOBID2 ≥ 3)	3.19 (1.94-5.24)	<0.001
ADL function	1.03 (0.98-1.09)	0.213
Quality of life (QUALIDEM)	0.89 (0.86-0.92)	<0.001
Depression (CSDD)	1.21 (1.15-1.27)	<0.001
Number of prescribed drugs	1.10 (1.03-1.17)	0.005
Sleep disturbances	4.51 (2.91-6.99)	<0.001
Appetite disturbance	3.46 (1.65-7.27)	0.001
Agitation/aggression	5.37 (3.21-8.97)	<0.001
Depression (NPI-NH)	4.49 (2.73-7.37)	<0.001
Anxiety	4.60 (2.67-7.93)	<0.001
Apathy	2.27 (1.38-3.73)	0.001
Disinhibition	2.65 (1.45-4.83(	0.001
Aberrant motor behavior	3.51 (1.72-7.17)	0.001
Euphoria	3.30 (1.39-7.85)	0.007
Irritability	6.27 (3.95-9.96)	<0.001
Delusion		
Pain (MOBID2 ≥ 3)	2.89 (1.75-4.76)	<0.001
ADL function	1.01 (0.95-1.07)	0.773
Quality of life (QALIDEM)	0.89 (0.86-0.92)	<0.001
Depression (CSDD)	1.22 (1.17-1.28)	<0.001
Number of prescribed drugs	1.11 (1.04-1.20)	0.003
Sleep disturbances	4.06 (2.57-6.42)	<0.001
Appetite disturbance	3.13 (1.49–6.55)	0.003
Agitation/aggression	5.47 (3.06-9.81)	<0.001
Depression (NPI-NH)	4.29 (2.56-7.20)	<0.001
Anxiety	4.28 (2.47-7.42)	<0.001
Apathy	2.17 (1.27-3.69)	0.004
Disinhibition	3.03 (1.70-5.39)	<0.001
Aberrant motor behavior	3.02 (1.51-6.05)	0.002
Euphoria	4.03 (1.69-9.65)	0.002
Irritability	6.41 (3.87-10.61)	<0.001
Hallucinations		
Pain (MOBID2 ≥ 3)	2.78 (1.23-6.28)	0.014
ADL function	1.19 (1.07-1.33)	0.001
Quality of life (QALIDEM)	0.88 (0.84-0.93)	<0.001
Depression (CSDD)	1.15 (1.09-1.22)	<0.001
Number of prescribed drugs	1.09 (1.01-1.18)	0.029
Sleep disturbances	5.02 (2.55-9.90)	<0.001
Appetite disturbance	4.33 (1.87-10.02)	0.001
Agitation/aggression	3.67 (1.90-7.11)	<0.001
Depression	2.91 (1.36-6.22)	0.006
Anxiety	4.17 (2.05-8.48)	<0.001
Apathy	2.02 (0.91-4.48)	0.082
Disinhibition	1.37 (0.56-3.31)	0.490
Aberrant motor behavior	3.32 (1.61-6.84)	0.001
Euphoria	1.40 (0.30-6.57)	0.668
Irritability	2.56 (1.29-5.08)	0.007

Abbreviations: ADL, activities of daily living; CSDD, Cornell Scale of Depression in Dementia; MOBID2 indicates Mobilization-Observation-Behavior-Intensity-Dementia-2 pain scale; QUALIDEM, Quality of Life in Dementia.

[a]Logistic regression, with associations adjusted for age, sex, dementia diagnose, and cognitive function.

necessary in the acute setting where the resident can cause harm to himself and others, but the use of antipsychotics in treatment of psychosis in a chronic phase is a more complex matter. Guidelines state that non-pharmacological options such as environmental and psychosocial measures should be first-line treatment for psychosis in a chronic phase before antipsychotics are used, but few concrete suggestions are made.[39] Knowledge about the effect of non-pharmacological measures on psychosis is scant, and few studies have been performed.[43] In a study conducted by Chen et al in 2014, it was found that delusions and hallucinations in 104 older Taiwanese men with dementia were reduced in response to an organized program of non-pharmacological measures.[44] The number of patients was low, however, and the study only included men.[44] Arguments can be made that residents using antipsychotic medication have a more severe degree of psychosis than residents not using antipsychotics do. However, this does not seem to be the case in our study as there were no significant difference in the total NPI-NH score of psychosis for residents with psychosis using any antipsychotic medication and those who did not use any antipsychotic medication (Figure 2). When interpreting the results regarding antipsychotic medication, it is important to have some limitations mind. Residents with psychosis experienced more behavioral disturbances such as aggression than residents without psychosis. The use of antipsychotic medication such as Risperidone, and in some cases Haloperidol in delirious residents, are recommended in treating aggression, and there is a possibility that some of the use of antipsychotic medication in the psychosis group are due to aggression and not psychosis. The number of antipsychotic medication used in order to treat psychosis may therefore be lower than the total number of antipsychotics prescribed in residents with psychosis symptoms. One also has to take into consideration the somewhat low number of residents and the design of the study, but the findings are an important stepping stone for future studies. The efficacy of non-pharmacologically treatment approaches to psychosis is a key point that needs further investigations.

We also found that the total number of drugs was associated with symptoms of psychosis. Polypharmacy is a well-known challenge in NH residents and increases the risk of hospital admission, circulatory and endocrine comorbidity and neurological motor dysfunction.[45] The number of drugs also increases the possibility of anticholinergic side effects, such as confusion and delirium.[46] Delirium is often hard to distinguish from psychosis and has many of the same symptoms such as delusion and hallucinations.[15] Our findings support the hypothesis that psychosis is associated with polypharmacy, and they highlight the importance of a thorough medication review by physicians so as to avoid unnecessary drug prescription and development of possible debilitating side effects.

The association between pain and psychosis is supported to a certain degree by previous studies. Tosato et al found an association between pain and delusion in NH residents with cognitive impairment; however, they did not find an association between pain and hallucinations.[14] An explanation for this is perhaps the use of different assessment tools for psychosis symptoms, as the NPI-NH is more suited to detect and differentiate between psychosis symptoms than the minimum data set residents assessment instrument. Our own findings suggest that symptoms of psychosis, especially delusions, were ameliorated in response to pain treatment in residents with behavioral disturbances and dementia.[17] In contrast to the present study, we did not find a cross-sectional association between pain and symptoms of psychosis. A reason for this may be the more selected group of residents in the 2016 study, as it consisted of NH residents with dementia and behavioral disturbances. Our findings have clinical importance in that they indicate the need for a thorough pain assessment before making treatment decisions for residents with psychosis. If psychosis is caused, or triggered, by an underlying treatable factor such as pain, then treatment of this factor can ameliorate the symptoms of psychosis without the need for antipsychotic medication. Pain as a cause for NPS can be treated using a stepwise protocol for treating pain or a multidisciplinary approach, which has shown an effect in previous studies.[47–49] Our findings are cross-sectional, however, and there is a need to look at the association of pain and psychosis over time to gain more solid knowledge.

4.1 | Strengths and limitations

One of the strengths of this study is the broad inclusion criteria where all NH residents are 65 years of age and above, a life expectancy of more than 6 months and without schizophrenia were included. The greatest limitation lies perhaps in the cross-sectional design of the study, which cannot differentiate properly between psychosis in an acute and chronic setting and makes conclusions on causality difficult. More longitudinal studies are needed to draw conclusions on causality. Another limitation regarding the design of the study is that it is based on secondary analysis from an already existing database, where power calculations were made on the basis of other assessment tools and designs than our study. Therefore, there is a possibility that our study group may be underpowered. As it is not clear-cut which symptoms are possible confounders, the regression analyses were not adjusted for the impact of other NPS. This is a limitation, which is important to keep in mind when interpreting the results. There is also a lack of information regarding the cause of psychosis in residents without dementia, which is a limitation. The assessment of many of the outcome measures were made by proxy raters who knew the resident well. While studies have shown this to be an accurate assessment, especially for symptoms of psychosis, it cannot replace self-report for other symptoms such as pain.

5 | CONCLUSION

Symptoms of psychosis in NH residents lead to poorer QoL, more sleep disturbance, and are associated with pain and number of prescribed drugs. The use of antipsychotic medication in treatment of psychosis symptoms is associated with poorer QoL. The findings highlight that a thorough and broad evaluation of possible underlying causes should be made before making treatment decisions on chronic psychosis in NH residents.

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STUDY REGISTRATION

ClinicalTrials.gov (NCT02238652), Committee for Medical Ethics, Norway (2013/1765).

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10.6 Paper 3

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Original Study

Managing Pain and Psychosis Symptoms in Nursing Home Patients: Results from a Cluster-Randomized Controlled Trial (COSMOS)

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A B S T R A C T

Objectives: In nursing homes (NHs), 30% to 60% of patients experience daily pain and >80% have dementia. This can lead to neuropsychiatric symptoms, including psychosis symptoms such as delusion. We investigated if there was a relationship between pain and psychosis symptoms over time. We also aimed to investigate the effect of a multicomponent intervention (COSMOS) on pain, psychosis symptoms, and analgesic prescription.

Design: COSMOS is a cluster-randomized, single blinded, controlled trial. Each NH unit was defined as a cluster and randomized to either the COSMOS intervention or care as usual. The COSMOS intervention is a multicomponent intervention, consisting of staff training in communication, pain treatment, medication review, organization of activities, and safety. The intervention lasted for 4 months with a follow-up at month 9.

Setting and Participants: Sixty-seven units from 33 Norwegian NHs in 8 municipalities. The study included 723 patients aged ≥65 years, residing at the NH ≥2 weeks before inclusion. Patients with a life expectancy <6 months were excluded.

Measures: Pain was measured using the Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale. Psychosis symptoms were measured using the Neuropsychiatric Inventory–NH version. Measurements were performed at baseline, and months 4 and 9.

Results: Multilevel Mixed-Effect statistical analysis found that psychosis symptoms as a group (odds ratio [OR] 2.03, $P = .009$), and delusion (OR 2.12, $P = .007$) were associated with pain over time. No significant intervention effect on psychosis symptoms was observed. Compared with the control group, people with dementia in the intervention group experienced less musculoskeletal pain (β: −0.47, $P = .047$). Analgesic prescription was not affected by the intervention.

Conclusion and Implications: Pain is associated with psychosis symptoms, and pain assessment should be done when making treatment decisions on psychosis symptoms in NH patients. The COSMOS intervention improved musculoskeletal pain in people with dementia, but not psychosis symptoms, and there is need for further studies on treatment of psychosis symptoms in NH patients.

The nursing home (NH) population is heterogenic, with people experiencing many different acute and chronic conditions; over 80% have dementia.[1] Pain is common, and 30% to 60% of NH patients suffer from daily pain.[2,3] People with dementia are at risk of having untreated pain due to difficulties in reporting their own pain location and pain intensity, and this can in turn lead to reduced quality of life (QoL) and increased neuropsychiatric symptoms (NPS).[4–6] Due to these difficulties, physicians and nurses often have to rely on proxy rating or observation of behavioral signs to assess and treat the pain.[7]

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More than 90% of people with dementia experience at least 1 NPS during the course of their disease.[8] Such symptoms can be detrimental for patients, family, and caregivers alike and seriously affect patients' QoL.[9,10] NPS can be grouped together in clusters according to coexistent symptoms, such as agitation, mood, and psychosis, the latter consisting of delusion and hallucination.[11,12] Psychosis symptoms are common in an NH, with prevalence varying between 14% and 30%,[13,14] and are often the result of dementia or delirium.[15] Studies have previously found that psychosis symptoms in people with dementia are associated with reduced QoL and admission to an NH.[16–18] An association between pain and delusion, but not hallucinations has also been found.[19,20]

Psychosis symptoms can be triggered by different medications that can cause unwanted side effects, such as delirium.[15,21] Further, polypharmacy is common in an NH population, and studies have shown that regular medication reviews are necessary to decrease the risk of unnecessary drug prescriptions, as well as unwanted side effects.[22,23] Guidelines on the treatment of psychosis symptoms recommend nonpharmacological measures as the first-line approach and highlight the importance of treating possible underlying causes.[24,25] Previous studies have found that other NPSs, such as agitation, can benefit from nonpharmacological measures; however, the effect on psychosis symptoms is uncertain.[26] If nonpharmacological measures are insufficient, treatment with antipsychotics is recommended in the acute phase for a limited time.[24,25] Several studies, including a randomized placebo-controlled discontinuation trial of antipsychotic medication by Ballard et al.,[27] have found that mortality increases and QoL is reduced in patients receiving antipsychotic medication.[28]

Systematic assessment and treatment of pain have the possibility to benefit more than pain.[29–31] Husebo et al.[29] investigated the effect of systematic pain treatment on agitation in people with dementia, where agitation was reduced in response to pain treatment. Secondary analyses from the same study also show positive effects on mood symptoms as well as psychosis symptoms.[30,31]

The COSMOS trial was designed to improve the QoL of NH patients through better COmmunication, Systematic assessment and treatment of pain, Medication review, Organization of activities and Safety, thus the acronym COSMOS.[32,33] As the intervention included elements that previous studies have found to improve both pain and psychosis symptoms, we aimed to analyze whether the multicomponent intervention could improve pain and psychosis symptoms in people with and without dementia. We hypothesized that the intervention would have a positive effect on both pain and psychosis symptoms. We also wanted to determine if the use of analgesics changed in response to the intervention, as well as the characteristics, such as QoL, of patients with pain using analgesics.

Further, baseline data from the COSMOS study found an association between pain and psychosis symptoms[19]; we aimed to investigate if this association persisted over time by analyzing the control group patients who received their usual care.

Methods

This study was based on secondary analyses from the COSMOS trial. The study was a multicenter cluster-randomized, single blinded controlled trial performed from 2014 to 2015, aimed at improving patients' QoL through the implementation of a multicomponent intervention. The study enrolled 723 patients from 33 NHs and 67 different NH units in Norway. The entire study protocol and a description of the COSMOS intervention have previously been published in full elsewhere,[32,33] hence a summary is presented.

Inclusion and Exclusion Criteria

Patients ≥65 years who had stayed at the NH for at least 2 weeks were included. Patients with a <6 months' life expectancy were excluded from the study.

Randomization and Intervention

Each NH unit was defined as a cluster and randomized to receive either the COSMOS intervention or care as usual. The COSMOS intervention components were based on current state-of-the-art evidence,[7,26,34–36] and was implemented through a 2-day education seminar for NH staff, as well as a medication review for all units during the intervention period. All NHs participated with at least 2 staff members who were put in charge of implementing the COSMOS intervention at their respective NH units. The intervention period lasted for 4 months, with a follow-up at month 9. Data collection was performed at baseline, month 4, and month 9. All assessments were performed by NH staff who knew the patient well.

Outcome Measures

Pain was assessed using the Mobilization-Observation-Behavior-Intensity-Dementia-2 (MOBID-2) Pain Scale. The scale has been thoroughly tested for validity, reliability, and responsiveness.[37,38] MOBID-2 consists of 2 parts, where part 1 assesses musculoskeletal pain through 5 actively guided movements during which the raters are encouraged to look for pain behavior. Part 2 consist of 5 items and assesses pain coming from head, skin, and internal organs. For each item, raters assess the patients' pain on a Numerical Rating Scale (NRS) from 0 to 10, where 0 represents no pain and 10 represents the worst pain possible. Finally, raters take all assessments into account and rate the patient's total pain score on an NRS from 0 to 10. A total pain score ≥3 is viewed as clinically significant pain.

Psychosis symptoms were measured using the Neuropsychiatric Inventory–Nursing Home Version (NPI-NH).[39] The NPI-NH measures the frequency and severity of 12 different NPSs (eg, agitation, delusion, and depression in the last week before assessment). Frequency (F) is measured on a scale from 0 to 4, where 0 represents not present, and 4 represents present daily. Severity (S) is measured on a scale from 1 to 3, where 1 represents mild symptom severity and 3 represents a severe symptom with high stress on the patient. The scores for frequency and severity are multiplied to generate a score for each symptom ranging from 0 to 12. A score ≥4 is considered a clinically significant symptom.[40] Previous factor analyses of NPS have found different symptom clusters, among others the psychosis symptom cluster, which consists of delusion and hallucinations.[11,12]

Other secondary outcome measures include the Cornell Scale for Depression in Dementia (CSDD),[41] and the Quality of Life in late-stage Dementia (QUALID).[42] Information concerning medication and diagnoses were obtained from the patients' medical records. Analgesics were defined as the group N02 in the Anatomical Therapeutic Chemical (ATC) classification system, which was further subdivided into opioid analgesics (N02A) and nonopioid analgesics (N02B and N02C). In addition, cognitive function was assessed using the Mini Mental State Examination (MMSE).[43]

Statistics

Analyses were performed by TFH in collaboration with a statistician (JM). The intervention effect on pain and psychosis were analyzed using Multilevel Mixed-Effect Linear Regression, with random

intercept for clusters and time as a categorical variable. The association between pain and psychosis over time in the control group was investigated using Multilevel Mixed-Effect Logistic regression with maximum likelihood estimation and random intercept for clusters. A clinically significant symptom of psychosis, representing the presence of 1 or more symptoms of psychosis, was defined as the dependent variable, and a clinically significant MOBID-2 score (≥3) was established as an independent variable. The same analysis was conducted for the individual symptoms of psychosis. Associations were adjusted for the effect of time, defined as a categorical variable, age, dementia severity, and use of opioids. Model fit was evaluated using Akaikes Information criterion.[44]

Ethics

Information about the COSMOS study and its implications was provided for all patients. Consent was obtained in written and verbal form from patients with the cognitive ability to provide it. For patients lacking this ability, presumed consent was obtained from the patients' next of kin or legal guardian after explaining the study procedure. The trial was approved by the Regional Committee for Medical and Health Research Ethics, West Norway (REK 2013/1765) and registered at clinicaltrials.gov (NCT02238652).

Results

A total of 723 patients were enrolled; 178 were excluded, leaving 545 patients to be included in the study. A total of 297 patients were randomized to the intervention group, with 248 allocated to the control group. A total of 73.8% of patients were women, with an average age of 86.7 years (Table 1).

There was no significant intervention effect on the total score of the MOBID-2 Pain Scale from baseline to month 9 (β −0.23; 95% confidence interval |CI| −0.88 to 0.42; $P = .49$) (Table 2). A significant positive intervention effect was found for MOBID-2 part 1 for people with dementia from baseline to month 9 (β −0.45; 95% CI −0.90 to −0.01; $P = .047$), but not for MOBID-2 part 2 (Figure 1). The number of patients using opioids increased nonsignificantly from baseline to month 9 in both groups, from 31.5% to 38.0% in the control group (odds ratio |OR| 1.31; $P = .20$) and from 30% to 35% in the intervention group (OR 1.26; $P = .27$). There was no significant intervention effect on the use of opioid analgesics (OR 0.95; 95% CI 0.53–1.70; $P = .86$).

The number of people with pain in the intervention group who did not use analgesics decreased from 24.3% to 19.4% from baseline to month 4, and remained stable at month 9 (Table 3). The number of people in the control group with a MOBID-2 score ≥3 who did not use analgesics steadily increased from baseline (19.1%) to month 9 (26.3%) (Table 3). The difference between the control and intervention groups, and changes within groups were not significant at either time point (Table 3). Patients in the intervention group with a MOBID-2 score ≥3 who used analgesics experienced more NPS (F 5.7; $P = .001$) compared with patients with a MOBID-2 score <3 at baseline and month 4 (Table 4). In the control group, the same was found at month 9 (F: 4.5; $P = .005$), but no such difference was observed at baseline and month 4 (Table 4). Patients with a MOBID-2 score ≥3 using analgesics had lower QoL than other patients at all time-points in both the control and intervention groups (Table 4).

Pain and psychosis symptoms as a group (OR 2.03; 95% CI 1.19–3.45; $P = .009$), and delusion individually (OR 2.12; 95% CI 1.23–3.63; $P = .007$) were significantly associated over time. There was no significant association between pain and hallucinations (OR 1.47; 95% CI 0.66–3.29; $P = .35$). Patients who used antipsychotic medication were more likely to experience pain than patients not using antipsychotic medication (OR 1.78; 95% CI 1.02–3.10; $P = .043$). There was no significant intervention effect on psychosis symptoms—either as a cluster (β 0.23; 95% CI −0.92 to 1.37; $P = .70$) or for the individual symptoms delusion and hallucinations (Table 2).

Table 1
Baseline Characteristics

Item	Control (n = 248)	Intervention (n = 297)	P Value	Total (n = 545)
Women (%)	186 (75.0)	216 (72.7)	.548	402 (73.8)
Age (SD)	87.0 (7.2)	86.5 (7.7)	.405	86.7 (7.5)
Weight in kg (SD)	63.4 (14.3)	64.5 (14.1)	.388	64.0 (14.2)
Height in m (SD)	1.64 (0.09)	1.63 (0.09)	.288	1.64 (0.09)
Dementia diagnosis (%)	155 (62.5)	196 (66.0)	.396	351 (64.4)
MMSE (SD)	11.4 (7.9)	10.4 (7.6)	.172	10.8 (7.8)
FAST (SD)	5.5 (1.4)	5.6 (1.4)	.187	5.6 (1.4)
ADL total (SD)	16.9 (5.5)	17.7 (5.2)	.099	17.4 (5.3)
Regular drugs (SD)	7.8 (3.8)	8.0 (3.8)	.466	7.9 (3.8)
CMAI total (SD)	42.6 (15.5)	42.0 (15.1)	.729	42.3 (15.3)
NPI-total score (SD)	17.9 (21.1)	17.5 (19.5)	.737	17.7 (20.2)
Psychosis cluster (SD)	2.9 (5.5)	2.3 (4.4)	.213	2.6 (4.9)
Delusion (%)	48 (21.0)	46 (16.0)	.149	94 (18.2)
Hallucinations (%)	24 (10.2)	23 (8.1)	.396	47 (9.0)
Agitation/Aggression (%)	54 (22.5)	71 (24.6)	.577	125 (23.6)
Depression (%)	46 (19.7)	79 (27.7)	.033	125 (24.1)
Anxiety (%)	58 (24.5)	66 (23.2)	.725	124 (23.8)
Euphoria (%)	10 (4.2)	10 (3.4)	.639	20 (3.8)
Apathy (%)	28 (11.8)	50 (17.4)	.075	78 (14.9)
Disinhibition (%)	37 (15.5)	50 (17.2)	.599	87 (16.4)
Irritability (%)	77 (32.1)	91 (31.4)	.862	168 (31.7)
Aberrant motor behavior (%)	32 (13.3)	29 (10.0)	.233	61 (11.5)
Nighttime disturbance (%)	44 (18.3)	63 (21.6)	.331	107 (20.1)
Appetite disturbance (%)	20 (8.5)	26 (9.1)	.818	46 (8.9)
Cornell total score (SD)	7.5 (6.6)	6.8 (5.7)	.484	7.1 (6.1)
MOBID-2 total score (SD)	2.8 (2.8)	2.3 (2.4)	.106	2.5 (2.6)
Analgesic drugs (%)	156 (62.9)	165 (55.6)	.083	321 (58.9)
Opioids (%)	78 (31.5)	89 (30.0)	.708	167 (30.6)
Psychotropic drugs (%)*	177 (71.4)	209 (70.4)	.903	386 (70.8)
Antipsychotics (%)	30 (12.1)	48 (16.2)	.177	78 (14.3)
Anxiolytics (%)	58 (23.4)	56 (18.9)	.195	114 (20.9)
Hypnotics And Sedatives (%)	79 (31.9)	82 (27.6)	.279	161 (29.5)
Antidementia drugs (%)	38 (15.6)	44 (15.2)	.898	82 (15.4)
Antidepressants (%)	99 (40.6)	119 (41.0)	.914	218 (40.8)

ADL, Activities of Daily Living; CMAI, Cohen Mansfield Agitation Inventory; FAST, Functional Assessment Staging.
*N05A, N05B, N05C, N06A, N06D in the ATC-register.

Discussion

Pain was significantly associated with psychosis symptoms, and delusion over time, but not with hallucinations. This is important for clinicians, as it suggests that a thorough pain assessment is essential before making treatment decisions concerning psychosis symptoms. This is to our knowledge the first study to investigate the relationship between pain and psychosis symptoms over time. The COSMOS intervention had a positive effect on musculoskeletal pain in people with dementia, highlighting the importance of a thorough pain assessment and treatment strategy in NHs.

The total MOBID-2 pain score was not reduced in response to the COSMOS intervention. Musculoskeletal pain was, however, reduced in people with dementia. The reason that musculoskeletal pain was reduced in people with dementia in the intervention group compared with the control group, and not for the total population, can be explained by the ability of the MOBID-2 pain scale to detect pain in people with dementia. Patients without cognitive impairment are able to report their own pain and the effect of pain treatment, or lack thereof, which assists the physician's decision making.[7] The assessment of musculoskeletal pain can also be more straightforward compared with the assessment of pain from the internal organs, head, and skin, as musculoskeletal pain can be provoked by active

Table 2
Effect of Intervention Compared With Control on Pain and Psychosis Symptoms*

Item	Total Population					
	Baseline to Month 4			Baseline to Month 9		
	β-coefficient	95% CI	*P* Value	β-coefficient	95% CI	*P* Value
MOBID-2 total score	−0.11	−0.74 to 0.53	.740	−0.23	−0.88 to 0.42	.490
MOBID-2 part 1	−0.07	−0.50 to 0.35	.734	−0.40	−0.84 to 0.05	.079
MOBID-2 part 2	−0.12	−0.40 to 0.15	.369	−0.02	−0.30 to 0.26	.885
Psychosis cluster-total	−0.19	−1.29 to 0.91	.736	0.23	−0.92 to 1.37	.696
Delusion	−0.06	−0.80 to 0.68	.872	0.19	−0.57 to 0.96	.619
Hallucinations	−0.06	−0.63 to 0.50	.823	0.01	−0.58 to 0.59	.979
	Patients With dementia					
MOBID-2 total score	−0.14	−0.80 to 0.51	.668	−0.23	−0.89 to 0.43	.495
MOBID-2 part 1	−0.13	−0.57 to 0.30	.545	−0.45	−0.90 – −0.01	**.047**
MOBID-2 part 2	−0.11	−0.39 to 0.16	.421	−0.09	−0.37 to 0.19	.531
Psychosis cluster-total	−0.23	−1.39 to 0.92	.694	0.28	−0.91 to 1.48	.646
Delusion	0.07	−0.71 to 0.85	.852	0.41	−0.40 to 1.22	.326
Hallucinations	−0.24	−0.83 to 0.35	.419	−0.18	−0.79 to 0.43	.567

Note: Bold values are statistically significant ($P < .05$).
*Analyzed using Multilevel Mixed-Effect Linear Regression.

movements, as in part 1 of the MOBID-2 Pain Scale. Our findings are partly in line with a previous study by Sandvik and colleagues,[45] who found that a Stepwise Protocol for Treating pain reduced pain in NH patients with dementia and behavioral disturbances. However, in contrast to our study, this study focused primarily on the treatment of pain and found an intervention effect on the total pain score, not only on musculoskeletal pain.[45] In the COSMOS study, no significant intervention effect on pain was found, although the number of patients with pain increased over time in the control group and decreased in the intervention group. This may suggest that the intervention group could have benefited from the COSMOS intervention to a certain degree.

The use of analgesics was high in both groups, especially the number of patients using opioids on a regular basis, which increased from 30% to >35% from baseline to month 9 in both the control group and intervention group. A previous study found a rise in the use of opioids in Norwegian NHs from 2000 to 2011, from 1.9% to 17.9%.[46] Our findings suggest that this trend has continued, which is particularly worrisome considering the possible side effects from long-term opioid use and risk of polypharmacy in people with dementia.[47,48] A recent study by Erdal et al.[49] investigating the effect of analgesic treatment on depression in NH patients with dementia found that patients being prescribed a buprenorphine transdermal patch had a significantly higher chance of dropping out of the study due to adverse events. This highlights the importance of being thorough in evaluating the risk of possible side effects in patients, before and during the prescription of an opioid analgesic.

When investigating the characteristics of patients with and without pain using and not using analgesics, we observed that patients with pain who used analgesics had lower QoL and more NPS than other patients. This supports previous studies, which have found pain to be associated with NPS and poor QoL.[5,50] However, it was unexpected that no significant differences were found between patients' QoL scores concerning those with pain using analgesics and those with pain not using analgesics, as the aim with analgesic prescription is to reduce the patient's pain and improve their QoL. In future studies, this could be an important focus point when investigating the effect of long-term analgesic use in NH patients. If

Fig. 1. Progression of pain scores (MOBID-2) in people with dementia. MOBID-2 part 1: Musculoskeletal pain (Significant invention effect), MOBID-2 part 2: Pain from internal organs, head, and skin.

Table 3
Use of Analgesics in People With and Without Clinically Significant Pain (MOBID-2 ≥3)

	Control (n = 202)		Intervention (n = 251)	
Baseline (χ^2 Control vs. Intervention: $\chi^2 = 4.08$, $P = .253$)				
	MOBID-2 ≥3	MOBID2 <3	MOBID-2 ≥3	MOBID2 <3
Uses analgesics (% of pain group)	76 (80.9)	57 (52.8)	78 (75.7)	65 (43.9)
No analgesics (% of pain group)	18 (19.1)	51 (47.2)	25 (24.3)	83 (56.1)
Month 4 (χ^2 Control vs. Intervention: $\chi^2 = 5.19$, $P = .158$)				
	Control (n = 185)		Intervention (n = 208)	
	MOBID-2 ≥3	MOBID2 <3	MOBID-2 ≥3	MOBID2 <3
Uses analgesics (% of pain group)	64 (77.1)	51 (50.0)	58 (80.6)	61 (44.9)
No analgesics (% of pain group)	19 (22.9)	51 (50.0)	14 (19.4)	75 (55.1)
Month 9 (χ^2 Control vs. Intervention: $\chi^2 = 4.20$, $P = .241$)				
	Control (n = 174)		Intervention (n = 184)	
	MOBID-2 ≥3	MOBID2 <3	MOBID-2 ≥3	MOBID2 <3
Uses analgesics (% of pain group)	56 (73.7)	49 (50.0)	51 (79.7)	54 (45.0)
No analgesics (% of pain group)	20 (26.3)	49 (50.0)	13 (20.3)	66 (55.0)

long-term use of opioid analgesics causes more harm through unwanted side effects than benefit, more focus on frequent reevaluation of long-term use of opioid analgesics is needed.

As hypothesized, psychosis symptoms and pain were associated over time, as was the individual symptom delusion, but not hallucinations. This is in line with previous cross-sectional findings from the baseline data of the COSMOS study.[19] Previous studies have found a cross-sectional association between pain and delusion, such as Tosato et al.,[20] who found a relationship between pain and delusion in 2822 NH patients with dementia from 8 countries. As this is the first study that investigates the longitudinal relationship between pain and psychosis symptoms, our finding adds important knowledge regarding psychosis symptoms in NH patients. If psychosis symptoms, and especially delusion, are associated with pain, then a thorough assessment of pain should be a prerequisite when deciding on treatment options for psychosis symptoms, and aid in reducing the use of psychotropic medication to those who benefit the most from them. This is further highlighted by our finding that use of antipsychotic medication was associated with pain. If psychosis symptoms are triggered by underlying pain, then treatment of the underlying factor would be preferred rather than treating only the overt symptoms.

In contrast to our hypothesis, no significant intervention effect on psychosis symptoms was found. This diverges from a previous study from 2016, where systematic pain assessment and treatment in 352 patients with dementia and behavioral disturbances reduced psychosis symptoms.[18] It is important to keep in mind that only 94 (18%) patients in the COSMOS study experienced at least 1 psychosis symptom at baseline,[19] limiting the potential to discover an intervention effect. The 2 studies also differ regarding the type of intervention. Where the 2016 study only focused on systematic pain assessment and treatment, this was only 1 part of the COSMOS trial, which includes components with the ability to reduce psychosis symptoms, such as organization of activities and medication review. Despite this, psychosis symptoms were not reduced, which underlines the complexity in treating psychosis symptoms in NH patients and that there is no one-size-fits-all treatment. Guidelines state that nonpharmacological options should be the first-line treatment, but knowledge concerning the effect of such treatments is sparse and our study is one of few that investigates the effect of nonpharmacological options.

Table 4
Characteristics of Different Pain-Analgesics Groups

Item — Mean (SD)	No Pain No Analgesics	No Pain Using Analgesics	Pain No Analgesics	Pain Using Analgesics	P Value*
	Baseline				
	Control				
NPI-Total score	14.8 (16.8)	12.0 (16.5)	10.5 (13.1)	20.0 (24.4)	.121
NPI-Psychosis score	2.6 (4.6)	1.4 (3.5)	1.4 (3.1)	3.4 (6.0)	.107
Cornell score	5.4 (5.6)	4.8 (4.4)	8.4 (5.6)	9.6 (7.5)[a]	<.001
MMSE total	11.0 (8.4)	11.5 (7.9)	13.0 (8.7)	12.4 (7.7)	.720
QUALID total	18.1 (5.5)	20.0 (6.6)	19.7 (7.1)	24.4 (8.2)[a]	<.001
	Intervention				
NPI-Total score	11.9 (14.5)	16.3 (19.3)	17.2 (17.3)	25.2 (23.9)[a]	.001
NPI-Psychosis score	1.1 (2.7)	1.4 (3.6)	2.3 (5.4)	4.2 (5.7)[a,b]	<.001
Cornell score	4.5 (4.1)	7.4 (6.4)	6.5 (5.5)	8.7 (6.2)[a]	.001
MMSE total	10.1 (7.0)	10.6 (7.8)	10.6 (6.6)	9.7 (7.9)	.902
QUALID total	19.3 (5.5)	20.2 (7.2)	20.4 (7.9)	24.6 (7.8)[a,b]	<.001
	Month 4				
	Control				
NPI-Total score	12.5 (16.6)	9.7 (15.0)	18.4 (20.3)	16.9 (17.7)	.126
NPI-Psychosis score	2.0 (3.6)	1.8 (3.9)	2.4 (5.3)	3.3 (5.1)	.313
Cornell score	5.9 (5.8)	5.9 (5.9)	7.2 (4.5)	8.1 (6.3)	.237
MMSE total	12.7 (8.1)	12.3 (7.2)	11.4 (7.8)	9.8 (8.2)	.270
QUALID total	18.6 (5.5)	19.9 (6.2)	20.6 (6.9)	23.4 (7.6)[a]	.001
	Intervention				
NPI-Total score	6.2 (6.9)	10.7 (13.2)	13.2 (9.5)	16.5 (18.9)[a]	.001
NPI-Psychosis score	0.7 (1.7)	0.9 (1.8)	3.5 (6.7)[a,b]	2.3 (4.2)[a]	.002
Cornell score	4.9 (5.3)	6.9 (5.0)	8.0 (6.1)[a]	8.8 (6.5)[a]	.014
MMSE total	10.5 (6.3)	11.3 (9.0)	10.9 (6.7)	10.8 (7.8)	.958
QUALID total	18.9 (6.0)	20.6 (7.1)	25.4 (7.5)	24.3 (8.6)[a,b]	<.001
	Month 9				
	Control				
NPI-Total score	14.6 (20.4)	8.9 (12.3)	23.3 (24.4)	22.3 (22.3)[a]	.005
NPI-Psychosis score	2.6 (4.9)	1.2 (2.6)	2.8 (6.1)	3.9 (5.2)	.082
Cornell score	5.4 (5.7)	5.1 (4.3)	7.9 (6.1)	10.1 (7.6)[a,b]	<.001
MMSE total	12.0 (7.0)	11.5 (7.8)	11.2 (10.4)	10.3 (8.3)	.764
QUALID total	17.9 (5.3)	20.2 (6.2)	22.2 (7.4)	24.7 (8.5)[a,b]	<.001
	Intervention				
NPI-Total score	12.8 (19.2)	15.1 (16.6)	10.3 (7.3)	19.0 (21.6)	.321
NPI-Psychosis score	1.9 (4.7)	1.9 (3.2)	0.5 (1.7)	2.5 (4.6)	.529
Cornell score	5.0 (3.7)	6.7 (4.9)	5.7 (5.6)	9.0 (6.7)[a]	.009
MMSE total	10.5 (6.6)	9.4 (7.5)	11.7 (8.5)	8.7 (7.8)	.499
QUALID total	20.4 (7.3)	21.1 (6.4)	19.1 (4.7)	24.6 (8.9)[a]	.011

*One-way analysis of variance (with Bonferroni correction for multiple tests).
[a]Significantly different from the No Pain — No Analgesics group.
[b]Significantly different from the No Pain — Using Analgesics group.

Strengths and Limitations

This is one of the largest multicomponent intervention studies performed in a NH setting, and it includes a broad NH population both with and without dementia. This increases the generalizability of our findings. There is also a strength in using the MOBID-2 Pain Scale, which has been thoroughly tested for reliability and responsiveness for change. A limitation is that the study was powered with respect to QoL and not for pain and psychosis symptoms. It is a limitation that we only had data on type of pharmacological pain treatment, not dosage, or if nonpharmacological measures had been taken. There was also no assessment concerning the type of psychosis, or if the psychosis symptoms were chronic or acute in nature. A limitation also lies in the lack of knowledge regarding the duration of current pain and pain

treatment at baseline, which is important to consider when interpreting the results.

Conclusions and Implications

Pain, psychosis symptoms as a group, and delusion were significantly associated over time, highlighting the importance for clinicians to assess pain when making treatment decisions on psychosis symptoms. The COSMOS intervention had no significant effect on psychosis symptoms. The COSMOS intervention had a significant effect on musculoskeletal pain in patients with dementia, but not on the total pain score, which shows the need for systematic pain assessment and treatment in patients with dementia. The use of opioid analgesics increased in both groups and was not affected by the COSMOS intervention, which shows the importance of frequent reassessment of opioid prescriptions.

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