

# Efficacy and safety of analgesic treatment for depression in nursing home patients with dementia

Ane Erdal

Thesis for the Degree of Philosophiae Doctor (PhD)  
University of Bergen, Norway  
2019

UNIVERSITY OF BERGEN



# **Efficacy and safety of analgesic treatment for depression in nursing home patients with dementia**

Ane Erdal



Thesis for the Degree of Philosophiae Doctor (PhD)  
at the University of Bergen

2019

Date of defence: 10.01.2019

© Copyright Ane Erdal

The material in this publication is covered by the provisions of the Copyright Act.

Year: 2019

Title: Efficacy and safety of analgesic treatment for depression in nursing home patients with dementia

Name: Ane Erdal

Print: Skipnes Kommunikasjon / University of Bergen

## Scientific environment

This thesis was conducted from January 2014 to July 2018 at the Centre for Elderly and Nursing Home Medicine (SEFAS), in connection with the Research Group for General Practice (ALFO) and the Section for Elderly Medicine, Social Pharmacy and Interprofessional Workplace Learning (FEST) at the Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen. During this time, I have participated in courses and meetings offered by the Norwegian Research School in General Practice (NAFALM) and the Norwegian PhD School of Pharmacy (NFIF), where this work has been discussed. I have also had the opportunity to participate in the 2015 Training School “Treating pain in the frail elderly with dementia” in Ghent, organized by the European COST Action TD1005 “Pain Assessment in Patients with Impaired Cognition, especially Dementia”, and the 3<sup>rd</sup> Nordic PhD Meeting in Social and Clinical Pharmacy held in Copenhagen in February 2017, where this work was presented and discussed.

The DEP.PAIN.DEM trial was funded by the Research Council of Norway programme for independent basic research projects in the field of Medicine, Health Sciences and Biology (FRIMEDBIO), grant number 221951.

Main supervisor: Professor Bettina Sandgathe Husebø, Centre for Elderly and Nursing Home Medicine, Department of Global Public Health and Primary Care, University of Bergen, and Municipality of Bergen

Co-supervisors:

Associate Professor Elisabeth Flo, Department of Clinical Psychology, University of Bergen

Professor Dag Årslund, Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, and Centre for Age-related Medicine, Stavanger University Hospital

---

## Acknowledgements

First and foremost, I would like to thank my main supervisor Professor Bettina S. Husebø who has initiated and obtained funding for this important project. I am grateful for the opportunity to specialize within nursing home medicine, which has been a field of particular interest for me since working at the Hospital Pharmacy in Bergen as a consultant pharmacist in the municipal health services. In this position, I participated in multidisciplinary medication reviews to assess the appropriateness of drugs prescribed to nursing home patients. When discussing these patients with the physicians and nurses, I learned of people with dementia who were suffering from very severe agitation and depression despite receiving multiple psychotropic drugs. This sparked my interest in research on the efficacy of pharmacological treatment for neuropsychiatric symptoms of dementia. Professor Husebø has provided continuous support which has been invaluable during the sometimes strenuous process of data collection, and while sharing her expertise she has also encouraged me to shape the direction and focus of this thesis according to my own interests and ideas.

I am highly grateful to Professor Husebø and my co-supervisors, Associate Professor Elisabeth Flo and Professor Dag Årslund, for their guidance, encouragement, and enthusiasm. Without their joint expertise, this thesis would not have been possible.

As co-authors, I would like to thank Professor Geir Selbæk and Sverre Bergh, MD, PhD, at the Centre for Old Age Psychiatric Research, Division of Mental Health Services, Innlandet Hospital Trust, who have kindly provided their own data for my first paper. Professor Clive Ballard at the University of Exeter has contributed to the planning of this project, and kindly shared his expertise as a co-author. Dagrund Daltveit Slettebø at the Biostatistics and Data analysis core facility, Department of Global Public Health and Primary Care, University of Bergen, must also be acknowledged as a co-author, particularly for her invaluable contributions to the statistical analyses.

My thanks also to Magne Solheim and Jannicke Igland, Department of Global Public Health and Primary Care, University of Bergen, who provided randomisation and

blinding lists and sample size calculation for the DEP.PAIN.DEM trial. My thanks also to the manufacturers of the DEP.PAIN.DEM study treatment, Kragerø Tablettproduksjon AS and Mundipharma Ltd., and their associates, in particular Anne Hopstock and Harald Undersrud, for their considerable contributions to this work.

I thank the Research Council of Norway for providing the funding for my PhD project. In addition, I have received a travel grant from the Norwegian Research School in General Practice which enabled me to visit Université d'Auvergne, Clermont-Ferrand, and King's College, London. I am grateful to Professor Gisèle Pickering, Université d'Auvergne, and Professor Dag Aarsland, King's College, for welcoming me as a guest researcher.

I particularly wish to thank all of the included participants, their families, and the nursing home staff who have laid the foundation for this work by agreeing to participate in the REDIC, COSMOS, and DEP.PAIN.DEM trials and devoting their time and efforts to data collection.

To all my colleagues at the Centre for Elderly and Nursing Home Medicine, University of Bergen, I am grateful for all the coffee breaks and interesting discussions we have had, as well as always being able to ask for your guidance and vent my frustrations underway. Camilla Kjellstadli, thanks for being an excellent office-mate and friend. In particular I wish to acknowledge fellow PhD candidate Kjersti Marie Blytt, without whose contribution to data collection I am certain that this study could never have been completed in its current form – and I could not have asked for better company and support during our times on the road for data collection.

To my friends, I am thankful for all the time you have spent in both one- and two-way discussions of my work, as well as always being there to motivate me and celebrate my small victories along the way.

To my family: my dear parents Grethe Førdestrøm Erdal and Martin Erdal, my sisters Ingunn, Hilde, and Vivi-Marie, and of course my partner Tristan - I am deeply

---

thankful for your encouragement, patience, and unwavering support which has been essential in completing this project.

---

# Contents

<b>SCIENTIFIC ENVIRONMENT</b> .....	<b>II</b>
<b>ACKNOWLEDGEMENTS</b> .....	<b>III</b>
<b>ABBREVIATIONS</b> .....	<b>IX</b>
<b>LIST OF PUBLICATIONS</b> .....	<b>XI</b>
<b>ABSTRACT</b> .....	<b>XII</b>
<b>SAMMENDRAG</b> .....	<b>XVII</b>
<b>1. INTRODUCTION</b> .....	<b>25</b>
1.1 DEMENTIA.....	25
1.1.1 <i>Types of dementia</i> .....	26
1.1.2 <i>Neuropsychiatric symptoms</i> .....	29
1.2 DEPRESSION.....	32
1.2.1 <i>Depression and dementia</i> .....	33
1.2.2 <i>Treatment of depression in people with dementia</i> .....	35
1.2.3 <i>Non-pharmacological treatment of depression in dementia</i> .....	38
1.3 PAIN.....	39
1.3.1 <i>Pain and dementia</i> .....	40
1.3.2 <i>Treatment of pain in people with dementia</i> .....	41
1.3.3 <i>Pain and neuropsychiatric symptoms in dementia</i> .....	47
1.4 THE PAIN-DEPRESSION DYAD.....	48
1.4.1 <i>Pain and depression in people with dementia</i> .....	49
1.4.2 <i>Treating pain to reduce depressive symptoms in dementia</i> .....	51
1.5 RATIONALE FOR THE DEP.PAIN.DEM TRIAL AND THIS THESIS.....	53
<b>2. AIMS OF THE THESIS</b> .....	<b>54</b>
<b>3. METHODS</b> .....	<b>55</b>



---

3.1	OUTLINE OF DATA SOURCES.....	55
3.2	ASSESSMENT SCALES.....	55
3.3	PAPER I.....	60
3.3.1	<i>Design</i> .....	60
3.3.2	<i>The REDIC study</i> .....	60
3.3.3	<i>The COSMOS study</i> .....	61
3.3.4	<i>Trial profile</i> .....	63
3.3.5	<i>Outcome variables</i> .....	64
3.3.6	<i>Statistics</i> .....	65
3.4	PAPERS II-III.....	66
3.4.1	<i>Design</i> .....	66
3.4.2	<i>The DEP.PAIN.DEM trial</i> .....	66
3.4.3	<i>Paper II</i> .....	70
3.4.4	<i>Paper III</i> .....	72
<b>4.</b>	<b>MAIN RESULTS.....</b>	<b>75</b>
<b>5.</b>	<b>DISCUSSION.....</b>	<b>80</b>
5.1	GENERAL CONSIDERATIONS.....	80
5.2	DISCUSSION OF STUDY METHODS.....	81
5.2.1	<i>Paper I: a cohort study</i> .....	81
5.2.2	<i>Papers II-III: a randomised placebo-controlled trial</i> .....	83
5.2.3	<i>Use of proxy rating scales</i> .....	84
5.2.4	<i>Sources of bias</i> .....	90
5.2.5	<i>Controlling for bias</i> .....	91
5.3	DISCUSSION OF THE RESULTS.....	92

---

5.3.1	<i>The course of depressive symptoms in dementia.....</i>	93
5.3.2	<i>The efficacy of analgesic treatment for depression in people with dementia.....</i>	93
5.3.3	<i>The DEP.PAIN.DEM trial: Adverse events and safety .....</i>	95
5.3.4	<i>Differentiation between symptoms of dementia, depression, and adverse events .....</i>	96
5.3.5	<i>Adverse effects of buprenorphine in people with dementia.....</i>	97
5.3.6	<i>Sedation and reduced daytime activity during buprenorphine use.....</i>	101
5.3.7	<i>Interaction between buprenorphine TDS and antidepressants .....</i>	101
5.3.8	<i>Challenges concerning research in people with dementia.....</i>	105
5.4	EXTERNAL VALIDITY .....	106
5.5	ETHICAL CONSIDERATIONS .....	107
	<b>CONCLUSIONS .....</b>	<b>111</b>
	<b>IMPLICATIONS AND FUTURE PERSPECTIVES.....</b>	<b>112</b>
	<b>REFERENCES.....</b>	<b>114</b>

## Abbreviations

ACB	Anticholinergic Cognitive Burden
AD	Alzheimer's disease
ATC	Anatomical Therapeutic Chemical classification system
BPSD	behavioural and psychological symptoms of dementia
CDR	Clinical Dementia Rating
CI	confidence interval
COSMOS	Communication, Systematic pain assessment and treatment, Medication review, Organised activities, and Safety
CSDD	Cornell Scale for Depression in Dementia
dAD	Depression in Alzheimer's disease
DEP.PAIN.DEM	Efficacy of pain treatment on depression in people with dementia
DS-DAT	Discomfort Scale – Dementia of Alzheimer Type
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> edition
GDS	Geriatric Depression Scale
GMPI	Geriatric Multidimensional Pain and Illness Inventory
GS	Gestalt Scale
HDRS	Hamilton Depression Rating Scale
IASP	International Association for the Study of Pain
ICD-10	International Classification of Diseases, 10 <sup>th</sup> revision
IQR	interquartile range
mADCS-CGIC	modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change scale
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MMSE	Mini-Mental State Examination
MOBID-2	Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale
NaSSA	noradrenergic and specific serotonergic antidepressant
NPI-NH	Neuropsychiatric Inventory – Nursing Home Version
NPS	neuropsychiatric symptoms
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PAINAD	Pain Assessment in Advanced Dementia scale
PGC-PIS	Philadelphia Geriatric Centre – Pain Intensity Scale
PRN	<i>pro re nata</i> ; “as needed”
RC	regression coefficient
REDIC	Resource Use and Disease Course in Dementia
SD	standard deviation
SES	standardised effect size
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TeCA	tetracyclic antidepressant

TCA

tricyclic antidepressant

TDS

transdermal drug delivery system

---

## List of publications

- Paper I** Erdal A, Flo E, Selbaek G, Aarsland D, Bergh S, Slettebo DD, Husebo BS. Associations between pain and depression in nursing home patients at different stages of dementia. *J Affect Disord* 2017;218:8-14.
- Paper II** Erdal A, Flo E, Aarsland D, Ballard C, Slettebo DD, Husebo BS. Efficacy and Safety of Analgesic Treatment for Depression in People with Advanced Dementia: Randomised, Multicentre, Double-Blind, Placebo-Controlled Trial (DEP.PAIN.DEM). *Drugs Aging* 2018;35(6):545-558.
- Paper III** Erdal A, Flo E, Aarsland D, Ballard C, Slettebo DD, Husebo BS. Tolerability of buprenorphine transdermal system in nursing home patients with advanced dementia: a randomized, placebo-controlled trial (DEP.PAIN.DEM). *Clin Interv Aging* 2018;13:935-46.

### Other publications not included in this thesis

Corbett A, Husebo BS, Achterberg WP, Aarsland D, Erdal A, Flo E. The importance of pain management in older people with dementia. *Br Med Bull* 2014;111:139-148.

*Reprints of Paper I-III were made with permission from the publishers. All rights reserved.*

## Abstract

About 60-80% of nursing home patients with dementia have neuropsychiatric symptoms such as depression, agitation, and sleep disturbances. These may be debilitating and detrimental to the person's quality of life. Both neuropsychiatric symptoms and pain become more frequent in people with advanced dementia. Because they have reduced ability to verbally express their symptoms, undiagnosed and untreated pain may trigger neuropsychiatric symptoms in these individuals.

Depression is one of the most prevalent neuropsychiatric symptoms in dementia, affecting approximately one of two persons in the course of dementia. Cross-sectional studies have found that about 20% of nursing home patients with dementia have clinically significant depressive symptoms which often persist over time, and many receive antidepressants. However, recent randomised placebo-controlled trials and meta-analyses have shown absence of benefit from antidepressant treatment and increased risk of adverse events in this population.

Our research group has previously conducted a randomised controlled trial to investigate whether a stepwise protocol for treating pain reduced agitation in nursing home patients with dementia and agitation. Secondary analyses suggest that analgesic treatment may also reduce mood symptoms such as depression and apathy. However, the trial was not placebo-controlled, depression was not the primary outcome, and many participants did not have depression. Therefore, this project was planned in order to follow-up previous results with a placebo-controlled design including people with dementia and depression.

The relationship between pain and depression has been called the *pain-depression dyad*, implying that the conditions often coexist and exacerbate each other. This relationship is even more complex in people with dementia and reduced ability to communicate. Many also have multimorbidity, and polypharmacy is a common problem which poses an additional risk for drug interactions and drug related harm. Therefore, pain treatment must be individually tailored in order to the patient's needs. While it is clearly inappropriate to treat all people with dementia and depression with a

single type and dose of analgesic drug to relieve possible pain, we have aimed to identify participants who may benefit from a stepwise protocol for treating pain while attempting to minimise the risk of harm.

This thesis consists of three papers, and aims to investigate the impact of pain on the severity and progression of depressive symptoms over time in nursing home patients at different stages of dementia, and to evaluate the efficacy and tolerability of analgesic treatment for depression in people with moderate to severe dementia and depression.

Data from three different studies constitute the source material for this thesis. Paper I combines prospective observational data from two cohorts: the REDIC (Resource Use and Disease Course in Dementia) population was followed for 6 months after nursing home admission. The COSMOS (*CO*mmunication, *S*ystematic pain assessment and treatment, *M*edication review, *O*rganised activities and *S*afety) population includes people with varying lengths of nursing home stay who were followed for 4 months after inclusion. Paper II and Paper III use data from DEP.PAIN.DEM (Efficacy of pain treatment on depression in people with dementia), a randomised, placebo-controlled trial which assessed the efficacy of analgesic treatment for depressive symptoms in nursing home patients with advanced dementia and depression.

### **Aims**

Paper I aims to determine whether the severity of pain and depressive symptoms were associated in people at different stages of dementia, and whether having pain at baseline was associated with future worsening of depression.

Paper II aims to determine the efficacy of a stepwise increase in analgesic treatment for depressive symptoms in nursing home patients with moderate to severe dementia and depression.

Paper III aims to assess the tolerability and adverse events of transdermally administered buprenorphine in nursing home patients with moderate to severe dementia and depression, and whether tolerability is affected by cognitive function and concomitant drug use.

## Methods

In Paper I, we used data from one prospective cohort study (REDIC) including 684 people aged  $\geq 65$  with assessments at baseline and after 6 months, and one randomised controlled trial (COSMOS) including 67 units (clusters) that were randomised to receive a complex intervention or care as usual. From the latter group, 248 participants aged  $\geq 65$  years with assessments at baseline and after 4 months were included in the analyses. In both studies, pain was assessed using the Mobilisation-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale, depression with the Cornell Scale for Depression in Dementia (CSDD), and cognitive function with the Mini-Mental State Examination (MMSE).

Paper II and Paper III present the primary and secondary analyses, respectively, from a randomised, placebo-controlled trial (DEP.PAIN.DEM) including 162 nursing home patients aged  $\geq 60$  years with moderate to severe dementia (MMSE  $\leq 20$ ) and depression (CSDD  $\geq 8$ ). Participants were prescribed an individual increase in analgesic treatment (paracetamol or buprenorphine), and were randomised to receive either active treatment or identical, inert placebo for 13 weeks with assessments at baseline, 6 and 13 weeks. In Paper II, the primary outcome was treatment effect on change in depressive symptoms (CSDD); secondary outcomes were treatment effect on change in pain (MOBID-2), and adverse events. Paper III included the 89 participants who were prescribed buprenorphine (active/placebo). The primary outcome was time to discontinuation of active treatment compared to placebo, controlling for cognitive function and concomitant drug use. Secondary outcomes were adverse events associated with discontinuation, and treatment effect on daytime activity during the first week of treatment, measured by continuous actigraphy recording for 7 days before and 7 days after treatment was started.

## Results



---

In Paper I, we found that pain was significantly associated with depressive symptoms (regression coefficient (RC) .48,  $p < 0.001$ ). The association was replicated in subgroups with mild, moderate, and severe cognitive impairment. In the group followed from admission, depressive symptoms decreased over time, and having less pain at follow-up was associated with a decrease in depressive symptoms (within-subject effect;  $p = 0.042$ ).

In Paper II, we found that active analgesic treatment was associated with more persistent depressive symptoms compared to placebo. While depressive symptoms did not decrease significantly during active treatment from 0-13 weeks (mean change - 0.66, 95% CI -2.27; 0.94), the placebo group had a significant improvement in the same period (mean change -3.30, 95% CI -4.68; -1.92). The estimated treatment effect on depressive symptoms from 0-13 weeks was significant in favour of placebo (RC 2.64,  $p = 0.013$ ). Paracetamol reduced pain significantly from 6-13 weeks (RC -1.11,  $p = 0.037$ ), but depressive symptoms did not improve secondary to reduced pain (RC 1.58,  $p = 0.313$ ). 23 of 44 participants (52.3%) who received active buprenorphine were withdrawn from the trial due to adverse events ( $p < 0.001$ ).

In Paper III, we found that those who received buprenorphine had 4.7 times increased risk of discontinuation compared to the placebo group ( $p = 0.004$ ). Adjusting for concomitant drug use, we found that the risk was further increased in those who used antidepressants. Use of antidepressants and buprenorphine ( $n = 14$ ) was associated with 21.6 times increased risk of discontinuation compared to antidepressants and placebo ( $p = 0.003$ ). 9 participants in active treatment (20.5%) and 2 in the placebo group (4.4%) were excluded due to sedation or somnolence ( $p = 0.022$ ). Those who received buprenorphine had a significant 21% reduction in daytime activity on the second day of treatment ( $p = 0.005$ ), and mean daytime activity decreased by 13% during the first week of treatment compared to placebo ( $p = 0.053$ ).

## **Conclusions**

Despite observing that pain reduction was associated with less depressive symptoms in people with dementia, we were unable to detect a beneficial effect of an intervention with analgesic treatment on depressive symptoms compared to placebo. Contrarily, active treatment was associated with more persistent depressive symptoms compared to placebo, possibly due to adverse effects. In more than half of those who received buprenorphine, adverse events were reported. Known adverse effects of buprenorphine include somnolence, agitation, and anorexia, which may easily be mistaken for symptoms of depression or dementia in a clinical setting. Buprenorphine appears to be poorly tolerated in people with dementia. The risk and benefit of prescribing buprenorphine, and other opioid analgesics, to people with dementia and pain warrants further investigation.

---

## Sammendrag

Rundt 60-80 % av sykehjemspasienter med demens har nevropsykiatriske symptomer som depresjon, agitasjon og søvnforstyrrelser. Disse kan være svært hemmende og redusere individets livskvalitet betraktelig. Både nevropsykiatriske symptomer og smerter forekommer hyppigere hos personer med langtkommen demens. Fordi de har redusert evne til å uttrykke symptomer verbalt, kan udiagnostisert og ubehandlet smerte utløse nevropsykiatriske symptomer hos disse personene.

Depresjon er ett av de vanligste nevropsykiatriske symptomene ved demens, og rammer omkring en av to personer gjennom demensforløpet. Tverrsnittstudier har funnet at omtrent 20 % av sykehjemspasienter med demens har klinisk relevante depresjonssymptomer som ofte vedvarer over tid, og mange behandles med antidepressiva. Imidlertid har flere større studier og metaanalyser av nyere dato funnet manglende effekt av antidepressiv behandling og økt risiko for bivirkninger i denne populasjonen.

Vår forskningsgruppe har tidligere gjennomført en randomisert placebokontrollert studie for å undersøke om en trinnvis protokoll for behandling av smerte reduserte agitasjon hos sykehjemspasienter med demens og agitasjon. Sekundære analyser tyder på at smertebehandling også kan redusere stemningssymptomer som depresjon og apati. Denne studien var ikke placebokontrollert, depresjon var ikke det primære utfallsmålet, og mange deltakere hadde ikke depresjon. Dette prosjektet ble derfor planlagt for å undersøke om tidligere resultater kan gjenfinnes i en placebokontrollert studie som inkluderer personer med demens og depresjon.

Forholdet mellom smerte og depresjon har blitt kalt *smerte-depresjonsdyaden*, dette innebærer at tilstandene ofte forekommer samtidig og virker gjensidig forverrende. Dette forholdet er enda mer komplekst hos personer med demens og redusert evne til å kommunisere. Mange har også multimorbiditet, og polyfarmasi er et vanlig problem som utgjør en tilleggsrisiko for legemiddelinteraksjoner og legemiddelrelaterte skader. Derfor må smertebehandling tilpasses personens individuelle behov. Det ville være u hensiktsmessig å behandle alle personer med demens og depresjon med ett enkelt

legemiddel for å lindre mulig smerte. Vi har forsøkt å identifisere personer som kan ha nytte av en trinnvis økning i smertebehandling, med minimal risiko for skade.

Denne avhandlingen består av tre artikler, og har som mål å undersøke effekten av smerte på alvorlighetsgraden og utviklingen av depresjonssymptomer over tid hos sykehjemspasienter med ulike grader av demens, og å evaluere effekten og tolerabiliteten av behandling med analgetika mot depresjonssymptomer hos personer med moderat til alvorlig demens og depresjon.

Data fra tre ulike studier utgjør kildematerialet til denne avhandlingen. Artikkel I kombinerer prospektive observasjonsdata fra to kohorter: REDIC-populasjonen (Ressursbruk og sykdomsforløp ved demens) ble fulgt i 6 måneder fra innleggelse på sykehjem. KOSMOS-populasjonen (*K*ommunikasjon, *S*ystematisk smertevurdering og -behandling, *M*edikamentgjennomgang, *O*rganiserte aktiviteter og *S*ikkerhet) inkluderer pasienter med varierende lengde på sykehjemsoppholdet som ble fulgt i 4 måneder fra inklusjon i studien. Artikkel II og Artikkel III bruker data fra DEP.PAIN.DEM-studien (Effekten av smertebehandling på depresjon hos personer med demens), en randomisert, placebokontrollert studie som undersøker effekten av smertebehandling på depressive symptomer hos sykehjemspasienter med langtkommen demens og depresjon.

## **Mål**

I Artikkel I undersøker vi om alvorlighetsgraden av smerte og depresjonssymptomer er assosiert hos personer med ulik grad av demens, og hvorvidt det å ha smerte ved oppstart er assosiert med fremtidig forverring av depresjon.

I Artikkel II undersøker vi effekten av en trinnvis økning av smertebehandling mot depressive symptomer hos sykehjemspasienter med moderat til alvorlig demens og depresjon.

I Artikkel III undersøker vi tolerabilitet og bivirkninger av transdermalt administrert buprenorfin hos sykehjemspasienter med moderat til alvorlig demens og depresjon, og hvorvidt tolerabiliteten påvirkes av kognitiv funksjon og samtidig legemiddelbruk.

---

## Metode

I [Artikkel I](#) brukte vi data fra en prospektiv kohortstudie (REDIC) som inkluderte 684 pasienter  $\geq 65$  år med målinger ved oppstart og etter 6 måneder, og en randomisert kontrollert studie (KOSMOS) som inkluderte 67 enheter (klynger) som ble randomisert til å motta en kompleks intervensjon eller fortsette behandling som før. Fra sistnevnte gruppe inkluderte vi data fra 248 pasienter  $\geq 65$  år med målinger ved oppstart og etter 4 måneder. I begge studier ble smerte målt med MOBID-2 (Mobilisation-Observation-Behaviour-Intensity-Dementia-2) smerteskala, depresjon med CSDD (Cornell skala for depresjon ved demens), og kognitiv funksjon med MMSE (Mini-Mental Status Evaluering).

[Artikkel II](#) og [Artikkel III](#) presenterer henholdsvis primære og sekundære analyser fra en randomisert, placebokontrollert studie (DEP.PAIN.DEM) som inkluderte 162 sykehjemspasienter  $\geq 60$  år med moderat til alvorlig demens (MMSE  $\leq 20$ ) og depresjon (CSDD  $\geq 8$ ). Pasientene fikk forskrevet en individualisert økning i smertebehandling (paracetamol eller buprenorfin), og ble randomisert til å motta enten aktiv behandling eller identisk, inaktiv placebo i 13 uker med målinger ved oppstart og etter 6 og 13 uker. I [Artikkel II](#) var hovedutfallsmålet effekten på endring i depressive symptomer (CSDD); sekundære utfallsmål var behandlingseffekten på endring i smerte (MOBID-2), og uønskede effekter. [Artikkel III](#) inkluderte de 89 pasientene som fikk forskrevet buprenorfin (aktiv/placebo). Hovedutfallsmålet var tid til seponering av aktiv behandling sammenlignet med placebo, kontrollert for kognitiv funksjon og samtidig legemiddelbruk. Sekundære utfallsmål var bivirkninger assosiert med seponering, og behandlingseffekten på dagtidsaktivitet under den første behandlingsuken, målt gjennom kontinuerlig aktigrafiregistrering fra 7 dager før til 7 dager etter behandlingsoppstart.

## Resultater

I [Artikkel I](#) fant vi at smerte var signifikant assosiert med depressive symptomer (RK (regresjonskoeffisient) .48,  $p < 0.001$ ). Assosiasjonen ble gjenfunnet i undergrupper

med mild, moderat og alvorlig demens. I gruppen av pasienter som ble fulgt fra sykehjemssinnleggelse falt depressive symptomer over tid, og redusert smerte ved oppfølging var assosiert med en samtidig reduksjon av depressive symptomer (individeffekt;  $p=0.042$ ).

I Artikkel II fant vi at aktiv smertebehandling var assosiert med mer vedvarende depressive symptomer sammenlignet med placebo. Mens depressive symptomer ikke falt hos gruppen som mottok aktiv behandling fra 0-13 uker (gjennomsnittlig endring - 0,66; 95 % KI (konfidensintervall): -2,27; 0,94), hadde placebogruppen en signifikant bedring i den samme perioden (-3,30; 95 % KI: -4,68; -1,92). Den beregnede behandlingseffekten viste signifikant bedring i placebogruppen (RK 2,64,  $p=0,013$ ). Paracetamol ga signifikant redusert smerte fra 6-13 uker (RK -1,11,  $p=0,037$ ), men depressive symptomer viste ingen bedring sekundært til denne smertereduksjonen (RK 1,58,  $p=0,313$ ). 23 av 44 pasienter (52,3%) som mottok buprenorfin ble trukket fra studien på grunn av uønskede hendelser ( $p<0,001$ ).

I Artikkel III fant vi at pasienter som mottok buprenorfin hadde 4,7 ganger økt risiko for seponering sammenlignet med pasienter i placebogruppen ( $p=0,004$ ). Justert for legemiddelbruk fant vi at risikoen var ytterligere økt hos pasienter som brukte antidepressiva. Bruk av antidepressiva og buprenorfin ( $n=14$ ) var assosiert med 21,6 ganger økt risiko for seponering sammenlignet med antidepressiva og placebo ( $p=0,003$ ). 9 pasienter i buprenorfingruppen (20,5 %) og 2 pasienter i placebogruppen (4,4 %) ble ekskludert på grunn av sedasjon eller somnolens ( $p=0,022$ ). Pasienter som mottok buprenorfin hadde en signifikant 21 % reduksjon i dagtidsaktivitet på 2. behandlingsdag ( $p=0,005$ ), og gjennomsnittlig dagtidsaktivitet ble redusert med 13 % i den første behandlingsuken sammenlignet med placebo ( $p=0,053$ ).

## **Konklusjoner**

Til tross for at vi fant at smertereduksjon var assosiert med reduserte depressive symptomer hos personer med demens, kunne vi ikke påvise noen bedring av

depressive symptomer ved behandling med analgetika sammenlignet med placebo. Vi fant det motsatte, nemlig at aktiv behandling var assosiert med mer vedvarende depressive symptomer sammenlignet med placebo, muligens på grunn av bivirkninger. Hos mer enn halvparten av pasientene som mottok buprenorfin ble det rapportert om uønskede hendelser. Kjente bivirkninger av buprenorfin inkluderer somnolens, agitasjon og anoreksi, disse kan lett forveksles med symptomer på depresjon eller demens i klinikken. Buprenorfin ser ut til å tolereres dårlig hos personer med demens. Risiko og nytte ved bruk av buprenorfin og andre opioidanalgetika hos personer med demens og smerter bør undersøkes videre.

---

# 1. Introduction

## 1.1 Dementia

Dementia is characterized by progressive neurodegenerative and/or vascular damage to the central nervous system, which causes impairment of memory and executive function. Neurodegeneration is a part of the normal aging process, and it is still unclear what causes these changes to develop to dementia in some individuals. As the amount of neurodegeneration increases with age, so does the incidence of dementia. In Western Europe, the prevalence of dementia in people aged 65-74 years is 4.6%, rising to 12.5% in those aged 75-84 years and 36.3% in those aged 85 years or more.<sup>1</sup> Thus, while dementia or “senility” is no longer regarded as a part of normal aging, it is inherently linked to old age, and the number of people living with dementia is expected to rise in the near future as a result of increased life expectancy and lower birth rates.<sup>1,2</sup>

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) criteria, dementia, or ‘major neurocognitive disorder’, can be diagnosed when a person experiences significant decline relative to previous performance in one or more cognitive domains such as language, learning and memory, or executive function, when these deficits interfere with their ability to function independently, and they cannot be explained by other causes like delirium or depression. The *International Classification of Diseases, 10th revision* (ICD-10) lists similar criteria for the dementia diagnosis. In addition, the ICD-10 requires a duration of minimum 6 months, combined with a decline in emotional control or motivation or a change in social behaviour. The latter criterion requires the presence of at least one of the following symptoms: emotional lability, irritability, apathy, or coarsening of social behaviour.

As reflected in these criteria, the progression of dementia leads to loss of independence – in fact, dementia is the leading cause of disability and need for chronic care in old age.<sup>3</sup> In 2015, the estimated annual global cost of dementia was



818 billion US\$, and approximately 47 million people were living with dementia worldwide.<sup>4</sup> This number is expected to nearly double every 20 years, and pass 131 million by 2050.<sup>1</sup> Much effort has been invested in research on potential drugs that can slow or cure the progression of dementia, but none have been successful. Acetylcholinesterase inhibitors or memantine may improve symptoms in mild to moderate dementia, but have no effect on disease progression.<sup>5</sup>

Being diagnosed with dementia is the strongest predictor of future admission to long-term nursing home care, and half of individuals with dementia are institutionalized after 5-6 years – generally because of a combination of impaired cognitive function, behavioural disturbances, and physical impairment.<sup>6-10</sup> In 2015, just short of 40 000 nursing home beds were registered in Norway, and 33 547 people were registered with long-term nursing home placement.<sup>11</sup> Recent estimates suggest that 84% of nursing home patients in Norway have dementia.<sup>12,13</sup>

### **Ongoing research and recent developments**

Work on this thesis started in January 2014. From 2014 to the present day of writing, 966 clinical trials related to the MeSH keyword ‘dementia’ were published in PubMed (MEDLINE) alone. A corresponding search for the combination ‘dementia’ and ‘depression’ retrieved 84 clinical trials, and the combination ‘dementia’ and ‘pain’ retrieved 14 clinical trials. This illustrates the rapid development of the evidence base. Although the rationale for the DEP.PAIN.DEM trial was well established based on existing literature at the time this work was commenced, the publications that are included in this thesis were influenced by more recently published works. The last literature search for this thesis was conducted in July, 2018.

#### **1.1.1 Types of dementia**

While general diagnostic criteria can identify people who are likely to have dementia, a definitive diagnosis of dementia can only be made through post mortem examination. Dementia is classified according to the process leading to loss of

---

neuronal function, which may be neurodegenerative, vascular, or secondary to other disease or injury.

### **Neurodegenerative dementia**

The most common cause of dementia in old age is Alzheimer's disease, which accounts for approximately 60% of all dementia cases.<sup>14</sup> The prevalence in nursing home patients may be higher, as a recent study found that 71% of people with dementia had Alzheimer's disease at admission to nursing home placement.<sup>13</sup> Although the pathogenesis is still unclear, Alzheimer's disease is characterized by deposition and accumulation of amyloid- $\beta$  peptide into extracellular plaques, and formation of intracellular neurofibrillary tangles due to hyperphosphorylation and aggregation of the tau protein.<sup>15</sup> These changes develop gradually over decades, starting long before any clinical symptoms become evident. The first region of the brain to be affected is the hippocampus, which is involved in the consolidation of new memories and in spatial orientation. The severity and rate of hippocampal atrophy can be used as a measure of the severity of Alzheimer's disease.<sup>16</sup> The next regions to be affected are the limbic system, which regulates functions such as emotion, pain processing, behaviour, motivation, and long-term memory, and the neocortex, which is involved in higher cognitive functions such as perception, spatial reasoning, conscious thought, and language.<sup>17-19</sup> The severity of damage to these regions is also closely correlated to cognitive impairment.<sup>20</sup>

Dementia with Lewy bodies is the second most common cause of neurodegenerative dementia, and accounts for approximately 20% of all recently diagnosed dementia cases according to updated diagnostic criteria.<sup>21,22</sup> However, the prevalence in nursing home patients may be lower, as a recent study found that only 4% of nursing home patients with dementia admitted to nursing home placement had Lewy body dementia.<sup>13</sup> The most prominent early symptoms are deficits in attention and executive function, with characteristic fluctuating alertness and cognitive performance, as well as impaired visuospatial ability.<sup>21</sup> Visual hallucinations and psychiatric symptoms such as depression, anxiety, and psychosis are common.

Parkinsonism may also be a feature of dementia with Lewy bodies, which is distinguished from dementia in Parkinson's disease by the temporal presentation of cognitive and motor impairment.

Other causes of neurodegenerative dementia include frontotemporal dementia and Huntington's disease, which – along with Alzheimer's disease – are leading causes of early-onset dementia. Early-onset dementia is associated with accelerated disease progression and high mortality. Frontotemporal dementia and Huntington's disease appear to follow a particularly malignant course.<sup>23</sup>

### **Vascular dementia**

Vascular damage is considered the second most common cause of dementia in elderly people, and has been estimated to account for 26% of all dementia cases.<sup>24,25</sup> In vascular dementia, neuronal damage is caused by a disruption in the blood vessels to the brain, which may be either haemorrhagic or ischemic due to infarction.<sup>26</sup> The clinical presentation of vascular dementia depends on the type, severity, and localization of vascular damage, as well as the presence of any other neurodegenerative damage. Although memory often is more preserved in vascular dementia compared to Alzheimer's dementia, the functional impairment may be more severe in vascular dementia because concurrent motor disability and mood symptoms are more frequent.<sup>26</sup>

Most people with late-onset Alzheimer's disease also have cerebrovascular lesions, and vascular damage is associated with more rapid progression of Alzheimer's dementia.<sup>27</sup> Vascular burden thus appears to play a part in the aetiopathogenesis of Alzheimer's pathology, and Alzheimer's dementia is not always clinically distinguishable from vascular dementia. Therefore, "mixed dementia" with Alzheimer's and vascular pathology has been suggested to be the most common type of dementia, representing the middle ground in a continuous spectrum from pure Alzheimer's to pure vascular pathology.<sup>14</sup>

---

## Secondary dementia

Dementia may less commonly develop as a secondary symptom of a pre-existing injury or disease process. Examples include Wernicke-Korsakoff syndrome, which is caused by thiamine deficiency and usually secondary to alcohol abuse.<sup>28</sup> Infections, such as human immunodeficiency virus (HIV), or traumatic or toxic brain injury are other less common causes of dementia.

### 1.1.2 Neuropsychiatric symptoms

In addition to progressive cognitive impairment, neuropsychiatric symptoms (NPS) or behavioural and psychological symptoms of dementia (BPSD) are a core component of the dementia syndrome, regardless of the cause of dementia. The terms NPS and BPSD can be used interchangeably, but while NPS is the preferred term in the United States, BPSD is used by the International Psychogeriatrics Association.<sup>29</sup> To clarify the similarities and differences between NPS and BPSD, the definitions are presented in Box 1.

Neuropsychiatric symptoms will be used here as an umbrella term which includes the following 12 individual symptoms: delusions, hallucinations, depression/dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleep disturbances, and appetite changes.<sup>30,31</sup> Nearly all people with dementia have clinically significant neuropsychiatric symptoms at some stage of the disease; these symptoms are often troublesome and are strong predictors of nursing home admission in addition to the severity of cognitive, functional and memory impairment.<sup>7,32</sup>

### **Box 1. Taxonomy for non-cognitive symptoms of dementia.**

#### **Behavioural and psychiatric symptoms of dementia (BPSD)**

*“...the term behavioural disturbances (should) be replaced by the term behavioural and psychiatric symptoms of dementia, defined as follows: Signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia.”*<sup>29</sup> Although the following simple grouping of symptoms was suggested in 1996, the symptoms and symptom clusters have not been exhaustively described and multiple assessment scales are recommended for measuring individual symptoms and symptom clusters.

- **Behavioural symptoms:** Usually identified on the basis of observation of the patient, including aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviours, sexual disinhibition, hoarding, cursing and shadowing.
- **Psychological symptoms:** Usually and mainly assessed on the basis of interviews with patients and relatives; these symptoms include anxiety, depressive mood, hallucinations and delusions.

#### **Neuropsychiatric symptoms (NPS)**

*“This taxonomy chooses an empirically based syndromic approach to taxonomy rather than the identification of individual ‘target’ symptoms (e.g., dysphoria or delusion) (...) This method begins by identifying individual symptoms in large populations of persons with Alzheimer’s disease, proceeds to analyse their inter-relationships, and then defines clusters of disturbance.”*<sup>33</sup> Suggested diagnostic criteria for an **‘affective’** and a **‘psychotic’** disturbance in Alzheimer’s disease were based on the co-occurrence and relative severity of

- **Affective symptoms:** depression; irritability; anxiety; euphoria.
- **Associated symptoms:** aggression; psychomotor agitation; delusions; hallucinations; sleep disturbance; appetite disturbance.

---

Neuropsychiatric symptoms occur in more than 80% of people with any type of dementia at some stage of the disease.<sup>34</sup> However, the prevalence and severity of individual neuropsychiatric symptoms may differ in accordance with the progression and underlying cause of dementia (i.e. the areas of the brain that are most affected). Environmental factors may also modulate the presentation of neuropsychiatric symptoms. For instance, in nursing home units that have a higher number of staff per patient and spend more time on patient care, there is a lower prevalence of apathy compared with units that have a lower care capacity.<sup>35</sup>

### **Person-centred care for neuropsychiatric symptoms in dementia**

Person-centred care is based on the assumption that the person with dementia has unique needs which are shaped in relation to their physical and psychosocial surroundings and the care provided.<sup>36</sup> The carer aims to identify unmet needs in order to improve quality of life for the person with dementia. Unmet psychosocial needs in nursing home patients with dementia may include aspects such as emotional distress, lack of emotional support, insufficient social interactions, loneliness, or need for day-time activities.<sup>36</sup> Physical and practical needs may include aspects of physical health, physical ability such as mobility, senses such as vision and hearing, self-care, accommodation, and so forth.<sup>36</sup> In the perspective of person-centred care, neuropsychiatric symptoms are viewed as expressions of unmet needs which consequently may be treated by successfully identifying and meeting the person's needs. For instance, while one person with dementia may thrive in a crowded environment, another person may experience confusion, anxiety or agitation due to sensory overstimulation in the same environment. A potential strategy to treat these symptoms may therefore be a change of environment to a quieter zone with one-to-one contact. Similarly, symptoms of agitation, aggression or depression in people with dementia may be exacerbated by untreated pain.<sup>37-39</sup>

The effectiveness of person-centred care for people with dementia has recently been investigated in a meta-analysis of nineteen interventional studies, which found

significant beneficial effects of the interventions on neuropsychiatric symptoms, agitation, depression, and quality of life.<sup>40</sup>

## 1.2 Depression

According to DSM-5 criteria, major depressive disorder is characterized by the core symptoms depressed mood (note: may be irritable mood in children/adolescents) and/or loss of interest or pleasure. In addition, changes in appetite or body weight, sleep pattern (insomnia or hypersomnia), psychomotor activity (agitation or retardation), fatigue or loss of energy, feelings of worthlessness or guilt, reduced ability to think, concentrate, or make decisions, and recurrent thoughts of death or suicidal ideation are listed as possible symptoms of depression. To fulfil the DSM-5 diagnostic criteria, five or more symptoms including at least one of the core symptoms must have been present during the same two-week period, and represent a change from previous functioning. Furthermore, the symptoms must cause clinically significant distress or reduced ability to function, and cannot be attributed to other physical or mental disease.

ICD-10 criteria describe similar symptoms typical of a depressive episode: lowered mood, reduced energy, decreased activity, impaired capacity for enjoyment, interest, and concentration, marked tiredness after even small efforts, disturbed sleep and diminished appetite, reduced self-esteem and self-confidence, and ideas of guilt and worthlessness. Furthermore, lowered mood in depression is described as fairly constant from day to day, unresponsive to circumstances, and may be accompanied by “somatic” symptoms such as: loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending on the number of symptoms present and their severity, depression may be classified as mild, moderate, or severe.

---

### 1.2.1 Depression and dementia

Depression is highly prevalent in all types of dementia, it is commonly one of the first presenting symptoms, and may even precede cognitive impairment as a prodromal or early symptom of a dementing disorder. In the most common dementia types, the patterns of neurodegenerative damage originate from the limbic system. Depression can be difficult to differentiate from early stages of dementia because the conditions share many core symptoms, such as lack of initiative, and impairment of memory and executive function.<sup>41</sup> In late-life depression, defined as a major depressive episode occurring in an elderly person (60 years or older), it has been estimated that as many as 20-50% present with reduced cognitive function compared to non-depressed controls with comparable age and education level.<sup>42-44</sup> While cognitive decline is progressive and irreversible in dementia, it should resolve completely upon successful treatment and remission of a depressive disorder. The now outdated term “depressive pseudodementia” has been used to describe such transient cognitive impairment caused by depression.<sup>44</sup> Large longitudinal studies have shown that although elderly people with depression show improvement of cognitive function when depression is successfully treated, they may not return to the level of function they previously had, and furthermore they are at higher risk of future conversion to mild cognitive impairment and dementia compared to elderly people without a history of depression.<sup>45,46</sup> Those who are older at depression onset, with lower baseline cognitive function and greater vascular burden, show less improvement in cognitive function upon remission.<sup>44,47</sup>

Due to differences in study design, assessment and definition of depression, estimates of depression prevalence vary widely between studies. A recent meta-analysis of neuropsychiatric symptoms in people with Alzheimer’s disease found a pooled depression prevalence of 42%, while estimates from single studies ranged from 19-78%.<sup>48</sup> Although fewer studies have assessed depression in other dementia types, available data suggest that depression is even more prevalent in vascular dementia and dementia with Lewy bodies compared to Alzheimer’s dementia.<sup>49</sup>



In 2002, Olin et al. suggested provisional diagnostic criteria for depression in Alzheimer's disease (Box 2).<sup>50</sup> The criteria were adapted from the DSM-4 diagnostic criteria for major depressive disorder, which were deemed unsuitable for direct application in people with Alzheimer's disease because they have been developed for patients with idiopathic psychiatric conditions, and greatly depend on the patient's ability to verbally report subjective depressive symptoms.<sup>50</sup> Furthermore, the authors described diagnostic challenges related to changes in behaviour such as loss of interest, withdrawal or social isolation which are not specific to depressed individuals with Alzheimer's disease, as these behaviours may also be observed in people with dementia but no apparent mood disturbance.<sup>50</sup>

Depression is often persistent or follows a fluctuating course in people with dementia.<sup>51-53</sup> Irrespective of dementia diagnosis, depression becomes more prevalent with increasing dementia severity,<sup>54</sup> causing increased suffering and reduced quality of life.<sup>55</sup> Comorbid dementia and depression is associated with a more accelerated decline in daily functioning and cognition, and may thus contribute to earlier loss of independence and need for nursing home placement.<sup>7,56,57</sup> Some evidence indicates that people with dementia and depression may be at risk of worse outcomes of medical treatment, such as rehabilitation after hip fracture, and increased mortality compared to those without depression.<sup>58-62</sup> In order to mitigate these effects, treatment of depression in dementia is a clinical priority.

**Box 2. Provisional diagnostic criteria for depression in Alzheimer’s disease. Olin et al., 2002 (excerpt)<sup>50</sup>**

**A.** Three (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either 1) depressed mood or 2) decreased positive affect or pleasure.

**Note:** Do not include symptoms that, in your judgment, are clearly due to a medical condition other than Alzheimer’s disease, or are a direct result of non-mood-related dementia symptoms (e.g., loss of weight due to difficulties with food intake).

- (1) Clinically significant depressed mood (e.g., depressed, sad, hopeless, discouraged, tearful)
- (2) Decreased positive affect or pleasure in response to social contacts and usual activities
- (3) Social isolation or withdrawal
- (4) Disruption in appetite
- (5) Disruption in sleep
- (6) Psychomotor changes (e.g., agitation or retardation)
- (7) Irritability
- (8) Fatigue or loss of energy
- (9) Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
- (10) Recurrent thoughts of death, suicidal ideation, plan or attempt

**B.** All criteria are met for Dementia of the Alzheimer type (DSM-IV-TR).

**C.** The symptoms cause clinically significant distress or disruption in functioning.

**D.** The symptoms do not occur exclusively during the course of a delirium.

**E.** The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication).

**F.** The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer’s disease, anxiety disorders, or substance-related disorder.

## 1.2.2 Treatment of depression in people with dementia

The Norwegian Directorate of Health published updated guidelines for diagnosing and treating dementia in 2017, which include recommendations for treatment of depression in dementia.<sup>63</sup> For people with mild cognitive impairment or dementia and mild/mild-to-moderate depression, environmental, psychosocial, and/or psychotherapeutic interventions are recommended as first-line treatment. Antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) should be offered as a supplement when needed, but only when individually tailored non-

pharmacological interventions have been attempted without the desired effect. For treating people with moderate/severe depression, non-pharmacological interventions are recommended in combination with offering treatment with an antidepressant of the SSRI class. These recommendations are graded as weak, meaning that benefits outweigh harms for the majority, but not for everyone.<sup>63</sup> In general, the guideline states that a weak recommendation could be based on unclear evidence for efficacy, or a finely balanced consideration of risk versus benefit. Therefore, the decision to start treatment will be influenced by other factors such as patient preference, comorbidity, polypharmacy, or burden of medical care.<sup>63</sup>

The Norwegian national guideline for treating depression in dementia corresponds to recommendations from other national guidelines, as presented in a recent review.<sup>64</sup> Although most guidelines recommend use of an SSRI, e.g. citalopram or sertraline, when antidepressant treatment is indicated, some suggest that other classes such as noradrenergic and specific serotonergic antidepressants (NaSSAs), e.g. mirtazapine, may also be of benefit.<sup>64</sup> SSRIs and NaSSAs are currently the most commonly used antidepressants in people with dementia and depression.<sup>64,65</sup> The efficacy of SSRIs for treating depression in people with dementia has been assessed in five placebo-controlled trials, while only one placebo-controlled trial has tested a NaSSA in this group (Table 1).

Lyketsos et al. included 44 patients with moderate to severe Alzheimer's disease and depression, and found a significant reduction in CSDD depression after 12 weeks of sertraline treatment compared to placebo (weighted mean difference -6.70, 95% CI -11.50; -1.90).<sup>66</sup> Contrary to this result, the four other studies did not find benefit of SSRI therapy. In a larger study by the same group, Rosenberg et al. included 131 memory clinic patients with mild to moderate Alzheimer's disease and depression, and found no improvement in CSDD after 12 weeks of sertraline treatment compared to placebo.<sup>67</sup> The largest study by Banerjee et al. included 326 patients from old-age psychiatry services with moderate dementia and depression. Participants were randomised in 1:1:1 ratio to receive treatment with sertraline, mirtazapine, or placebo for 39 weeks with follow-up at 13 and 39 weeks. After 13 weeks, CSDD had

**Table 1. Placebo-controlled trials of antidepressants in people with dementia.**

Antidepressant	Authors, year	Population	Duration	Scales	Findings
Imipramine (TCA)	Reifler BV et al., 1989, USA <sup>68</sup>	24 outpatients with AD (MMSE $\leq$ 25, mean MMSE 17.5) and depression (HDRS $\geq$ 15)	8 weeks	HDRS	No significant difference in improvement at completion of study or rate of improvement between active treatment and placebo.
Clomipramine (TCA)	Petracca GM et al., 1996, Argentina <sup>69</sup>	21 outpatients with probable AD (MMSE $\geq$ 10, mean MMSE 21.5) and depression (HDRS $>$ 10)	6 weeks	HDRS	In the treatment group, mean change was -10.70 (SD 7.36). In the placebo group, mean change was -4.50 (SD 8.31).
Moclobemide (MAOI)	Roth M et al., 1996, international <sup>70</sup>	511 in/outpatients with dementia (MMSE 12-27, mean MMSE 20.2) and depressive symptoms (GDS $\geq$ 5, HDRS $\geq$ 14)	7 weeks	HDRS	In the treatment group, mean decrease was 12.6 (CI 11.3/12.5) compared to 9.1 in the placebo group (CI 7.8/9.1), $p < 0.001$ .
Sertraline (SSRI)	Magai C et al., 2000, USA <sup>71</sup>	31 female NH patients with late-stage AD and probable depression; minor (CSDD $\geq$ 3) or major (CSDD $\geq$ 8)	8 weeks	CSDD, GS	No significant difference between sertraline and placebo.
Fluoxetine (SSRI)	Petracca GM et al., 2001, Argentina <sup>72</sup>	41 outpatients with probable AD (MMSE $\geq$ 10, mean MMSE 23.2) and depression (HDRS $\geq$ 14)	6 weeks	HDRS	No significant difference in improvement at completion of study or rate of improvement between active treatment and placebo.
Sertraline (SSRI)	Lyketsos CG et al., 2003, USA <sup>66</sup>	44 outpatients with probable AD (MMSE $\geq$ 10, mean MMSE 17.0) and major depressive episode (DSM-IV criteria).	12 weeks	CSDD and HDRS	Significant improvement in the active treatment group compared to placebo, measured with CSDD ( $p = 0.002$ ).
Venlafaxine (SNRI)	de Vasconcelos Cunha UG et al., 2007, Brazil <sup>73</sup>	31 outpatients $>$ 60 years old with dementia (MMSE 10-24) and depression	6 weeks	MADRS	No significant difference between venlafaxine and placebo.
Sertraline (SSRI)	Rosenberg PB et al., 2010, USA <sup>67</sup>	131 patients from memory clinic with AD (mean MMSE 20.0, SD 4.6) and dAD (median CSDD 13, IQR 9-18).	12 weeks	CSDD, mADCS-CGIC	No significant difference in improvement at completion of study or rate of improvement between active treatment and placebo.
Sertraline (SSRI) and mirtazapine (NaSSA)	Banerjee S et al., 2011, UK <sup>74</sup>	326 patients from old-age psychiatry services with dementia (mean MMSE 18.1) and depression (CSDD $\geq$ 8).	13 (39) weeks	CSDD	No significant difference in improvement at completion of study or rate of improvement between active treatment with either drug and placebo.

AD; Alzheimer's disease, CSDD; Cornell Scale for Depression in Dementia, dAD; Depression in Alzheimer's disease, DSM; Diagnostic and Statistical Manual of Mental Disorders, GDS; Geriatric Depression Scale, GS; Gestalt Scale, HDRS; Hamilton Depression Rating Scale, IQR; interquartile range, mADCS-CGIC; modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change scale, MADRS; Montgomery-Åsberg Depression Rating Scale, MAOI; monoamine oxidase inhibitor, MMSE; Mini-Mental State Examination, NaSSA; noradrenergic and specific serotonergic antidepressant, NH; nursing home, SSRI; selective serotonin reuptake inhibitor, TCA; tricyclic antidepressant.

improved significantly in all three groups, and was unchanged from 13 to 39-week follow-up. No significant between-group differences on CSDD were found.<sup>74</sup>

Systematic reviews and meta-analyses have concluded that there is no robust evidence to support the efficacy of antidepressants for depression in people with dementia.<sup>75-77</sup>

As expected from previous trials, Banerjee et al. found that the placebo group had significantly fewer adverse events compared to sertraline ( $p=0.010$ ) and mirtazapine ( $p=0.031$ ).<sup>74</sup> Although the number of deaths or serious adverse events did not differ significantly between active treatment and placebo, the risk of serious adverse events being rated as severe was higher in participants who received active treatment ( $p=0.003$ ).<sup>74</sup> Other trials have found that antidepressant use is associated with increased risk of adverse events such as falls, hip fracture, stroke, or death in elderly patients and people with dementia.<sup>78-81</sup>

Despite the apparently unfavourable risk-benefit ratio for antidepressants in people with dementia, 39% of nursing home patients with dementia in Norway currently use one or more antidepressants.<sup>82,83</sup> A review including studies of antidepressant or antipsychotic drug use in nursing home patients in Western Europe from 2009-2015 found that antidepressant use in people with dementia ranged from 20% (Italy) to 47% (Sweden).<sup>83</sup> The widespread use of antidepressants in people with dementia, despite unclear efficacy, demonstrates a clear need for better and safer treatment options for depression in this group.

### **1.2.3 Non-pharmacological treatment of depression in dementia**

Several non-pharmacological interventions such as psychological therapy, reminiscence therapy and personalized pleasant activities have been shown to reduce depressive symptoms in people with dementia.<sup>84-86</sup> As stated in national guidelines, non-pharmacological interventions are currently recommended as first-line treatment for mild-to-moderate depression in people with dementia.<sup>63,64</sup> Unfortunately, these interventions are not suitable for all individuals, and are not systematically

---

implemented in nursing home care, possibly due to barriers such as lack of staff training or time.<sup>87</sup>

In the framework of person-centred care, unmet needs such as pain, isolation or lack of meaningful activity may cause or exacerbate neuropsychiatric symptoms in dementia. Therefore, it may be assumed that symptoms such as depression may be treated by identifying and applying strategies to reduce unmet needs.<sup>40,88</sup>

### 1.3 Pain

The International Association for the Study of Pain (IASP) has defined pain as “*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*”<sup>89,90</sup> Furthermore, the definition explicitly states that “*pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. (...) It is unquestionably a sensation in a part or parts of the body but it is also always unpleasant and therefore also an emotional experience.*”<sup>89,90</sup>

Pain intensity and quality is multidimensional, affected by complex conscious and subconscious processes in the peripheral and central pain processing network. Because pain has sensory, cognitive, and affective aspects, the same pain stimulus may be experienced very differently in the same individual and between individuals depending on factors such as the individual’s expectations and experience of context for the pain. For these reasons, self-reported pain intensity is usually regarded as the gold standard in pain research.<sup>91</sup> Different quantitative scales including verbal or pictorial aids, e.g. pain faces or colour changes from green to red, have been developed to aid self-report of pain even in children or people with cognitive impairment. However, studies have found that in severe dementia, the ability to comprehend pain assessment scales and report pain reliably is affected.

The IASP definition of pain was criticized for relying on the verbal expression of pain, thus excluding those who were unable to describe their experience of pain.<sup>92</sup> In 2001, IASP added the following note to the definition in response to these concerns:

*“The inability to communicate in no way negates the possibility that an individual is experiencing pain and is in need of appropriate pain relieving treatment.”*<sup>93</sup>

### **1.3.1 Pain and dementia**

In moderate-to-severe dementia, the ability to verbally express pain becomes progressively impaired. Pautex et al. included 129 participants with severe dementia ( $CDR \geq 3$ ) and found that 69% were able to comprehend and use at least one of three pain assessment scales.<sup>94</sup> However, in the 50<sup>th</sup> percentile with most impaired cognitive function ( $MMSE \leq 6$ ) less than half had ability to self-report pain using any scale.<sup>94</sup> This shows that people with dementia may experience pain but lack the ability to understand, remember, and/or verbally describe the intensity, location, or quality of pain. Therefore, observational pain assessment scales are required to identify pain in people with advanced dementia who lack the ability to self-report pain reliably.<sup>95</sup>

As for depression, the estimated prevalence of moderate to severe pain in nursing home patients with dementia varies considerably between different studies due to methodological differences. Studies from nursing homes in Norway have found that approximately 50% or more of people with dementia suffer from moderate to severe pain, and up to 80% suffer from pain of any severity including mild pain.<sup>96-98</sup>

Because pain is difficult to identify in people with dementia, untreated pain is recognized as a major clinical concern in this group. Systematic reviews have found that nursing home patients with dementia receive significantly less analgesics compared to nursing home patients without dementia,<sup>99</sup> the same systematic difference has been found in acute care, e.g. after hip fracture.<sup>100</sup>

Dementia may impact the cognitive component of pain processing in several different ways. In severe dementia, the ability to anticipate painful stimuli, e.g. after injury or during medical procedures, is impaired. Reduced autonomic activation (e.g. heart rate elevation) has been shown in people with dementia compared to cognitively intact controls during experimentally inflicted pain.<sup>101-103</sup>

---

In Alzheimer's disease, the sensory cortex is unaffected until the very late stages of the disease, and there is no evidence for impaired perception of pain.<sup>91</sup> However, the regions of the brain that are affected are involved in pain processing. Some neurodegenerative damage may increase the sensitivity to pain. This includes decreased activity in the descending inhibitory pathways, and vascular pathology such as white matter lesions.<sup>104</sup> Damage to the limbic system may impair motivation for pain avoidance or lead to reduced understanding of pain, even though the detection of painful stimuli may still be intact.<sup>91,104</sup>

Although neurodegeneration in dementia may impact pain processing pathways, current evidence has not shown any consistent differences in pain thresholds or tolerance for different pain stimuli in people with dementia compared to controls.<sup>91,105</sup>

### **1.3.2 Treatment of pain in people with dementia**

As mentioned previously, systematic reviews have found significantly lower rates of analgesic use in people with dementia compared to those without dementia. However, several recent studies have reported similar rates of analgesic use in nursing home patients with and without dementia, with an overall increase in total analgesic use irrespective of cognitive state, and a shift towards increased use of opioid analgesics.<sup>106,107</sup> In Norway, the use of opioid analgesics in nursing home patients increased from 11% in 2000 to 24% in 2011, with a substantial increase in the use of strong opioids from 1.9% to 17.9%.<sup>106</sup> Furthermore, in the 2011 cohort, the same study found that the odds ratio for use of strong opioids in nursing home patients with dementia did not differ significantly compared to those without dementia.<sup>106</sup> A study including the entire population of Denmark in 2010 reported that nursing home patients with dementia were significantly more likely to receive opioid analgesics compared to nursing home patients without dementia (43 and 38%, respectively).<sup>108</sup> Reports from other countries have found that untreated pain remains a significant clinical problem in people with dementia. A study including 425 patients from 12 nursing homes in Austria in 2011-2012 found that despite having more pain, fewer of



the participants with cognitive impairment received scheduled analgesic prescriptions compared to those without cognitive impairment (36% and 58%, respectively).<sup>109</sup>

Paracetamol is the most widely used non-opioid analgesic in nursing home patients and people with dementia. In Norway, regularly scheduled paracetamol treatment among nursing home patients has risen from 23% in 2000 to 48% in 2011 ( $p < 0.001$ ).<sup>106</sup> This does not include doses administered *pro re nata* (PRN; “as needed”). In a sample of 383 patients from six nursing homes in Australia, 69% received paracetamol within the last 24 hours (regularly scheduled or PRN), and there was no significant difference in paracetamol use among patients with and without dementia (71.0% and 67.3%, respectively,  $p = 0.44$ ).<sup>107</sup>

### **Non-opioid analgesics**

Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are classified as non-opioid analgesics, meaning that they do not exert their analgesic effects on the opioidergic system. NSAIDs inhibit cyclooxygenase enzymes to reduce prostaglandin synthesis, thereby reducing vasodilation, inflammation, and pain. In elderly patients, NSAID use is associated with increased risk of gastrointestinal bleeding, cardiovascular events, and acute renal failure, and NSAIDs have clinically relevant interactions with many drugs that are commonly used in elderly patients.<sup>110</sup> NSAIDs are therefore not recommended for use in elderly patients according to consensus-based criteria for appropriate prescribing.<sup>111</sup> Paracetamol has a different mechanism of action, which has not yet been fully described, but involves activation of descending serotonergic pathways.<sup>112,113</sup> As a weak cyclooxygenase inhibitor, paracetamol also reduces prostaglandin synthesis.<sup>113</sup> Therefore it resembles NSAIDs in activity, and is preferred in elderly patients due to its more favourable adverse effect profile, although it is a weaker analgesic.<sup>113</sup>

### **Opioid analgesics**

Opioid analgesics are indicated for the treatment of acute and chronic malignant or non-malignant pain, and are considered the mainstay for treating severe nociceptive

---

pain. Opioids act by activation of  $\mu$ ,  $\kappa$ , and  $\delta$  opioid receptors which are distributed in the brain, spinal cord, and gastrointestinal tract. Activation of the  $\mu$ -receptor is the primary mechanism for dose-related analgesic effects as well as respiratory depression, while  $\kappa$ -activation is associated with other adverse effects such as hallucinations and dysphoria.<sup>114</sup>

Adverse effects of individual opioids are determined by their pattern of receptor selectivity and activation, but many unwanted effects are common to all analgesics in the opioid class. For example, opioids increase the muscular tone and reduce motility in the gastrointestinal system; this causes constipation which may be severe.<sup>115</sup> Furthermore, stimulation of the chemoreceptor trigger zone in the area postrema causes nausea and activates the vomiting centre.<sup>116</sup> Upon repeated use, tolerance is developed for many of the central adverse effects of opioids such as sedation and euphoria, as well as for the intended analgesic effect.<sup>117</sup> This may lead to demand for a gradual dose increase, and to risk of dependence. Withdrawal symptoms such as hyperalgesia, restlessness, hyperhidrosis, anxiety, convulsions, and interrupted sleep may occur if an opioid is discontinued abruptly after prolonged use.<sup>117</sup>

Respiratory depression is an adverse effect of  $\mu$ -receptor activation, caused by decreased  $p\text{CO}_2$  sensitivity of the respiratory centre on the surface of the medulla oblongata.<sup>118</sup> Respiratory depression is dose-dependent, but may occur in therapeutic doses. The development of tolerance to respiratory depression is lower than tolerance to analgesic effects. This leads to risk of respiratory arrest and death, particularly at high doses and/or in combination with other drugs that cause respiratory depression, such as barbiturates.

### **Buprenorphine**

Buprenorphine is a semi-synthetic opioid which acts as a partial agonist on the  $\mu$ -receptor and an antagonist on the  $\kappa$ -receptor.<sup>119,120</sup> Partial activation of the  $\mu$ -receptor exerts analgesic effects, while limiting the dose-related risk of respiratory depression.<sup>121,122</sup> The risk of opioid tolerance and addiction is also less than for full agonists; dependence is unusual and withdrawal symptoms are reported as mild when

buprenorphine TDS is used to treat pain.<sup>122,123</sup> Buprenorphine has high lipid solubility, and is more potent with a longer-lasting analgesic effect compared to morphine; therefore it has been formulated for continuous transdermal application which provides stable serum concentrations with administration every 7 days.<sup>122,124</sup> Buprenorphine transdermal system (TDS) is indicated for the treatment of chronic moderate to severe pain, and is available in Norway in doses from 5 µg/hour which is approximately equivalent to 10 mg morphine per 24 hours. In contrast, fentanyl TDS, which is the only alternative transdermal opioid, has a starting dose of 12 µg/hour – corresponding to approximately 20-35 mg morphine per 24 hours. Due to mainly hepatic metabolism and clearance, buprenorphine does not require dose adjustment in patients with renal impairment.<sup>125</sup> This has, along with the possibility of a low starting dose and gradual dose increase with relatively low risk of respiratory depression and dependence, positioned buprenorphine TDS as an appropriate choice of opioid analgesic in elderly patients, including those with dementia.

### **Efficacy and safety of analgesics in dementia**

Despite the high prevalence of painful conditions and increasing use of analgesics in people with dementia, few studies have tested the efficacy and safety of different classes of analgesic drugs in people with dementia.<sup>126</sup> Age-related physiological changes in combination with dementing illness, as well as comorbid disease burden, lead to a particularly complex clinical situation where adequate pain relief may be difficult to achieve without unacceptable adverse effects. Furthermore, the assessment of both pain intensity and adverse effects may be difficult in people with reduced ability to communicate verbally. Due to lack of clinical evidence, no guidelines for the treatment of pain in dementia currently exist.

To date, only three placebo-controlled trials have tested the efficacy of analgesic treatment for pain or other distressing symptoms in people with dementia, two of which tested paracetamol versus placebo. The first trial by Buffum et al. tested the comparative efficacy of paracetamol 650 mg administered in scheduled doses four times daily in combination with PRN placebo versus placebo in scheduled doses in

---

combination with PRN paracetamol 650 up to four times daily.<sup>127</sup> Pain was the primary outcome, assessed using the Discomfort Scale – Dementia of Alzheimer Type (DS-DAT).<sup>128</sup> The trial included 39 patients with severe dementia and diagnosis of a painful condition from 3 nursing homes, and had a double-blinded crossover design: each patient was treated under one condition for two weeks before switching to the other condition without a washout period. Because only four patients received PRN paracetamol during placebo treatment, the results can be interpreted as a comparison of the efficacy of scheduled paracetamol versus placebo for pain. No difference in pain was found between the groups treated with paracetamol 650 mg administered four times daily and PRN.<sup>127</sup> However, the authors state that the administered dose may have been inadequate to treat moderate to severe pain, e.g. associated with degenerative joint disease, with which 84% were diagnosed. The occurrence of elevated liver function tests was similar between conditions (one during active treatment; one during placebo); the study did not report other adverse events.<sup>127</sup>

The second trial by Chibnall et al. tested the efficacy of paracetamol 1000 mg administered three times daily on behaviour and emotional well-being (Dementia Care Mapping), agitation (CMAI), and use of as-needed psychotropic drugs in 25 nursing home patients with dementia.<sup>129</sup> The trial had a double-blind placebo-controlled crossover design; each patient received 4 weeks of active treatment and 4 weeks of placebo.<sup>129</sup> While active treatment significantly increased the time spent in activity and socializing with others, no positive effect was found on agitation or emotional well-being. Two adverse events were reported during treatment; none of which were deemed treatment-related. Use of as-needed psychotropic drugs was also unchanged.

Although the evidence from these two trials is insufficient to determine the efficacy of paracetamol for pain and distressing symptoms in people with dementia, paracetamol remains the first-line treatment for pain in this population due to its favourable safety profile.<sup>126</sup>

Only one previous placebo-controlled trial of opioid analgesics has been conducted in people with dementia. Manfredi et al. assessed the efficacy of a long-acting opioid (20 mg oxycodone or morphine per 24 hours) for agitation (CMAI) in 47 nursing home patients with advanced dementia and agitation.<sup>130</sup> The study had a single-blind placebo-controlled crossover design. Each patient initially received placebo for 4 weeks, followed by 4 weeks of active treatment. The patients and study nurses were blinded to treatment allocation. Of the 47 patients who were enrolled in the trial, 22 did not complete the eight-week treatment protocol. Eleven withdrew during the initial placebo phase, and 11 during active opioid treatment. The main reasons for discontinuation of treatment were unsteady gait (three patients during the placebo phase; four patients during opioid treatment), increased agitation (two patients during the placebo phase; two patients during opioid treatment) and infection (one patient during the placebo phase; two patients during opioid treatment).<sup>130</sup> Although the withdrawal rate was high, adverse events which caused withdrawal were equally frequent during the placebo and active conditions, suggesting that the opioid was well tolerated. Mild and transitory adverse events such as sedation and nausea were more frequent during active treatment, but the difference was not statistically significant. One important limitation to this trial is the substitution of oxycodone 20 mg/day for morphine 20 mg/day in participants who could not swallow tablets. Oxycodone is 1.3-2 times more potent than morphine.<sup>131</sup> The authors reported that 13 of the 25 participants who completed the 8-week treatment protocol received oxycodone, and 12 received morphine. However, the treatment allocation for those who discontinued treatment was not reported. Therefore, the dose-dependent tolerability and relative tolerability of oxycodone and morphine in people with dementia remain unknown.<sup>130</sup>

### **Concerns regarding opioid use in people with dementia**

The observed increase of opioid use in people with dementia during the last decades may signal that the attention towards assessment and treatment of pain and discomfort in dementia has improved. However, this trend may also be a cause for concern. While opioid analgesics definitely have their place in the treatment of acute severe nociceptive pain in people with dementia, the benefit-risk ratio is more

---

uncertain for long-term use in patients with moderate chronic pain. For example, an observational study of home-dwelling elderly patients in the USA has shown a dose-dependent association between opioid use and risk of hip fracture.<sup>132</sup> Available data on the safety profile of opioid analgesics in cognitively intact elderly patients may not be generalizable to people with dementia.

Buprenorphine TDS is a relatively new analgesic drug which has been available in Norway since 2005, and has quickly become one of the most frequently used opioid analgesics in nursing home patients and people with dementia in Scandinavia. In 2011, a study found that 10.5% of 1542 nursing home patients with dementia were prescribed buprenorphine TDS which accounted for 58% of the total use of strong opioids in this population.<sup>106</sup> A study of the entire population of Denmark in 2010 confirms this trend, showing that 12.3% of nursing home patients with dementia used buprenorphine TDS, while 27.8% used any strong opioid.<sup>108</sup>

Use of buprenorphine TDS for chronic moderate to severe non-malignant pain has been controversial, as opioids previously have been primarily indicated for cancer pain.<sup>133</sup> In people with dementia, very little is known about the prevalence of adverse effects such as sedation, somnolence, nausea, anorexia, hypotension, urinary retention, infection, gait disturbance, falls and hip fracture. Considering how rapidly use of buprenorphine TDS has grown in this population, the tolerability and adverse effects of buprenorphine in people with dementia warrants further investigation.

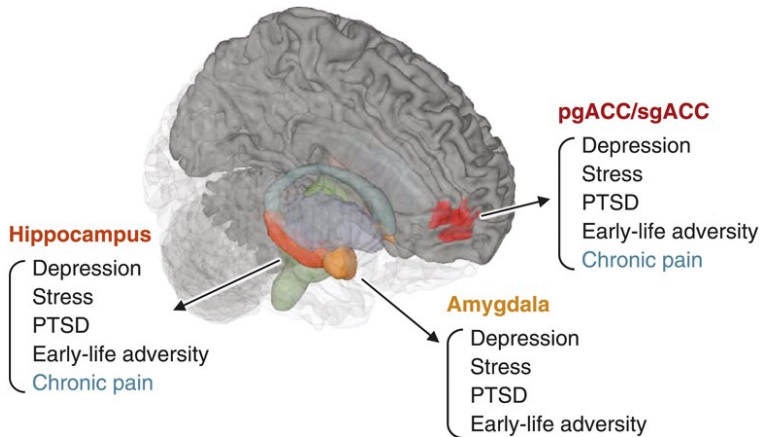
### **1.3.3 Pain and neuropsychiatric symptoms in dementia**

Chronic pain is associated with numerous adverse outcomes in elderly people, including depression, decreased socialization, sleep disturbance, increased healthcare utilization and cost, and risk of adverse effects from multiple drug prescriptions.<sup>134</sup> Although the consequences of pain are less well described in people with dementia, studies have found higher levels of neuropsychiatric symptoms in those with pain or discomfort compared to those without.<sup>135-137</sup>

At the time the DEP.PAIN.DEM trial was planned, three previous randomised controlled trials had investigated whether treating pain may reduce neuropsychiatric symptoms in nursing home patients with dementia.<sup>138-140</sup> Manfredi et al. included 47 participants in a double-blind placebo-controlled crossover trial of a long-acting opioid (oxycodone or morphine, 20 mg/day) for 4 weeks, and found no overall improvement in agitation.<sup>130</sup> Chibnall et al. included 25 participants in a double-blind placebo-controlled crossover trial of paracetamol (3000 mg/day) for 4 weeks, and found increased activity and social involvement during active treatment, but no decrease in agitation or improvement in emotional well-being.<sup>129</sup> Husebo et al. included 352 participants with behavioural disturbances in a cluster-randomised controlled trial of a stepwise protocol for treating pain, with treatment effect on agitation as the primary outcome.<sup>38</sup> Pain treatment had a significant beneficial effect on agitation and overall severity of neuropsychiatric symptoms compared with the control group which received usual treatment ( $p < 0.001$ ).<sup>38</sup> Secondary analyses of data from the trial suggest that analgesic treatment also reduced depressive symptoms and mood disturbances in the same population.<sup>39</sup>

## **1.4 The pain-depression dyad**

The affective networks of the brain overlap with the pain processing network, and the subjective experience of pain is partly determined by an emotional component. The close relationship between pain and depression is illustrated by studies showing that grey matter changes in certain regions of the limbic system (hippocampus, amygdala, and cingulate cortex) are associated with multiple conditions that are often comorbid with chronic pain, such as depression (Figure 1).<sup>141</sup>



**Figure 1. Structural changes in the limbic system associated with chronic pain and other related conditions.** PgACC/sgACC, pregenual/subgenual anterior cingulate cortex; PTSD, post-traumatic stress disorder. Reprinted with permission from Woo and Wager (Pain 2015).<sup>141</sup>

It is well established that patients with chronic pain are at higher risk of depression, and patients with depression are at higher risk of painful somatic complaints.<sup>142,143</sup> Although no clear aetiology has been established, the conditions are known to commonly coexist, mutually exacerbate each other, share common signal pathways and neurotransmitters, and respond to similar treatments.<sup>144</sup> This relationship has been called the pain-depression dyad.<sup>144</sup>

#### 1.4.1 Pain and depression in people with dementia

Only four previous studies have explored the association between pain and depression in nursing home patients with moderate to severe dementia (Table 2).<sup>145-149</sup> All four studies reported significant associations. However, the results are limited by the lack of validated proxy-rated instruments for the assessment of pain and/or depression in people with severe dementia. Furthermore, as the studies were all cross-sectional, we still do not know whether pain is associated with future worsening of depression, or vice versa, in people with dementia.



**Table 2. Studies reporting association between pain and depression in nursing home patients with dementia.**

Author, country	Setting and method	Rater	Assessment scales	Sample size	Result	Comments
Cipher et al. (2004), <sup>145</sup> USA	234 patients with dementia from 8 NHs, cross-sectional design	Gero-psychologist (after referral)	GMPI, GDS-15	168 patients with pain, number of patients with depression and with combined depression and pain not reported	SOR 3.2, 95% CI 1.8-5.9	Stage of dementia not reported. GDS-15 not validated in dementia. <sup>150</sup>
Williams et al. (2005), <sup>146</sup> USA	331 patients with dementia (mean MMSE 8.1), 222 from 35 RC/AL facilities and 109 from 10 NHs, cross-sectional design	Care supervisors	NRS/PGC-PIS, CSDD	70 patients with pain, 79 patients with depression, 30 patients with pain and depression	OR 2.3, SD 1.1-4.8	NRS/PGC-PIS not validated in NH patients with dementia. <sup>151</sup> Small NH sample.
Leong et al. (2007), <sup>147</sup> Singapore	358 patients from 3 NHs (42.9% severely cognitively impaired), cross-sectional design	Self-report/ NH carers	NRS/ PAINAD, GDS-15/ CSDD	In the subgroup of 126 communicative patients with severe cognitive impairment, 54 had pain, 75 had depression, and 39 had combined pain and depression	SOR 3.2, 95% CI 1.8-5.9	GDS-15 not validated in dementia. <sup>150</sup> Unclear which instruments have been used to assess pain and depression.
Malara et al. (2016), <sup>148</sup> Italy	233 patients (181 with dementia, 112 severely cognitively impaired) from 10 NHs, cross-sectional design	Self-report/ NH carers	Pain diagnosis, NRS/ PAINAD, CSDD	In the subgroup of 181 patients with dementia, 84 had pain and 113 had depressive symptoms, number of patients with combined pain and depression not reported	OR 2.2, 95% CI 1.2-4.2	The association between pain and depression was reported for pain diagnosis, not using pain score (NRS/PAINAD). The impact of cognitive function or use of analgesic/psychotropic drugs was not assessed.

AL; assisted living, GDS; Geriatric Depression Scale, GMPI; Geriatric Multidimensional Pain and Illness Inventory, NH; nursing home, NRS; numeric rating scale, OR; odds ratio, PAINAD; Pain Assessment in Advanced Dementia scale, PGC-PIS; Philadelphia Geriatric Centre – Pain Intensity Scale, RC; residential care, SD; standard deviation, SOR; self-calculated odds ratio reported by van Dalen-Kok et al (2015)<sup>152</sup>

---

The most recent study by Malara et al. included 233 participants at different stages of dementia. To assess pain, a combination of self-report (NRS) and proxy rating (PAINAD) was used, as well as diagnosis by a physician. However, the authors did not specify which of these assessments were used in the subsequent analyses.<sup>148</sup>

Only the study by Leong et al. reported pain and depression prevalence stratified by cognitive function, this study included 358 patients of whom 126 had severe cognitive impairment and were able to self-report pain using a numeric rating scale (NRS).<sup>147</sup> However, as this was primarily a prevalence study, the association reported in Table 2 (which has been obtained from a secondary meta-analysis) applies to the whole sample, irrespective of cognitive status.<sup>152</sup> Therefore we still do not know whether a potential causal relationship between pain and depression may be affected by the progression of dementia.

#### **1.4.2 Treating pain to reduce depressive symptoms in dementia**

If pain is associated with worsening of depressive symptoms in people with dementia, there may be potential to reduce depression in this group by treating pain. The previous cluster randomised trial by Husebo et al. lends some support to this theory.<sup>39</sup> The trial included 352 participants with moderate-to-severe dementia (Functional Assessment Staging score >4) and clinically significant agitation (Cohen-Mansfield Agitation Inventory (CMAI) score  $\geq 39$ ) from 60 units (clusters) in 18 nursing homes.<sup>39,153,154</sup> The intervention group (n=175) received an 8-week stepwise protocol for treating pain using paracetamol, buprenorphine, morphine, or pregabalin, followed by a 4-week wash-out period. The control group (n=177) received usual treatment. The study treatment was well tolerated, and only four of 40 participants who received an opioid (buprenorphine/morphine) were withdrawn because of adverse events.<sup>155</sup>

Secondary analyses assessed the impact of analgesic treatment on mood and depressive symptoms, and found that the intervention group had a moderate improvement in depression assessed by the NPI-NH depression item (SES=0.3,

p=0.025). There was also a large improvement in mood, assessed by the NPI-NH mood cluster (NPI-NH depression, anxiety, sleep disturbance, apathy, and appetite items; SES=0.6, p<0.001).<sup>14</sup> However, depression was not an inclusion criterion, and the pain intervention was not placebo-controlled. Therefore, the efficacy and safety of analgesic treatment for depression in nursing home patients with dementia should be investigated further, using a robust placebo-controlled design, including participants with clinically significant depressive symptoms.

### **Antidepressant effects of buprenorphine**

The opioid  $\kappa$ -receptor is expressed at high levels in the regions of the brain that regulate mood, motivation, and reward, such as the limbic system.<sup>156</sup> Activation of the  $\kappa$ -receptor causes dysphoria, increased anxiety, and aversion.<sup>157,158</sup> Although these effects may be beneficial during acute stress, prolonged  $\kappa$ -receptor activation during conditions such as prolonged or uncontrollable stress may be a contributing factor in the aetiology of depression.<sup>157</sup> In contrast,  $\kappa$ -receptor antagonists have shown anxiolytic and antidepressant effects in rodent models.<sup>159,160</sup> Emerging evidence suggests that  $\kappa$ -receptor antagonists such as buprenorphine may represent a novel strategy for antidepressant treatment.<sup>161</sup> Although few trials have been conducted in people with depression, some clinical evidence supports this hypothesis.<sup>162,163</sup>

Buprenorphine is currently being tested in at least two ongoing phase II trials for treatment of depression (ClinicalTrials.gov identifiers NCT02263248 and NCT02181231).<sup>164</sup> A recent placebo-controlled trial of buprenorphine in combination with samidorphan, a  $\mu$ -receptor antagonist, for treatment-resistant depression has shown promising results.<sup>165</sup>

---

## **1.5 Rationale for the DEP.PAIN.DEM trial and this thesis**

Based on the preexisting evidence-base, as summarized in this introduction, the DEP.PAIN.DEM trial and this thesis were based on the following hypotheses:

- (1) The pain-depression dyad exists in people with moderate-to-severe dementia; therefore, people with dementia and depression are likely to have more pain.
- (2) Undiagnosed and untreated pain may cause increased depression in nursing home patients with dementia.
- (3) A stepwise protocol for treating pain, using paracetamol or buprenorphine TDS, may effectively reduce depressive symptoms in nursing home patients with dementia and depression with low risk of adverse events.
- (4) Buprenorphine is expected to reduce depression more efficiently compared with paracetamol because of its central effects on mood.

## 2. Aims of the thesis

The overall aims of this thesis were to investigate the impact of pain on the severity and progression of depressive symptoms over time in nursing home patients at different stages of dementia, and to evaluate the efficacy and tolerability of analgesic treatment for depression in people with moderate to severe dementia and depression.

Each of the three papers contribute to the overall aims of the thesis as described by the following specific aims:

Paper I aims to determine whether the severity of pain and depressive symptoms were associated in patients at different stages of dementia, and whether having pain at baseline was associated with future worsening of depression.

Paper II aims to determine the efficacy of a stepwise increase in analgesic treatment (using paracetamol or buprenorphine) for depressive symptoms in nursing home patients with moderate to severe dementia and depression.

Paper III aims to assess the tolerability and adverse events of transdermally administered buprenorphine in nursing home patients with moderate to severe dementia, with particular emphasis on sedation, examining associations with cognitive function, age, gender, and concomitant drug use.

### 3. Methods

#### 3.1 Outline of data sources

This thesis includes three papers with varying methodology, source material, and inclusion and exclusion criteria. Although three different studies have contributed data to these three papers, as shown in Table 3, most of the assessment scales that were used in the papers were common for all three studies. In the following, the assessment scales that were used will be presented first, followed by the methods, settings, participants, and ethical considerations in connection with each of the three studies that have contributed data to this thesis, and finally a presentation of each of the three papers including the design, eligibility criteria, primary and secondary outcomes, and statistical analyses that were used.

**Table 3. Sources of data for Papers I-III.**

		<b>REDIC</b> Cohort study	<b>COSMOS</b> Cluster-randomised controlled trial	<b>DEP.PAIN.DEM</b> Randomised placebo- controlled trial
<b>Paper I</b>	Prospective observational study	X	X*	
<b>Paper II</b>	Randomised placebo- controlled trial			X
<b>Paper III</b>	Randomised placebo- controlled trial			X

\*Control group only. COSMOS; Communication, Systematic pain assessment and treatment, Medication review, Organised activities, and Safety, DEP.PAIN.DEM; Efficacy of pain treatment on depression in people with dementia, REDIC; Resource Use and Disease Course in Dementia

#### 3.2 Assessment scales

This thesis mainly uses data collected from people with moderate to severe dementia. In order to ensure comparability between people at all stages of dementia, the assessment scales used rely mainly on proxy reports from the patients' formal caregivers. All assessment scales used in the thesis are summarized in Table 4. In the following, the most important scales that have been used as outcome measures and/or inclusion criteria are discussed in more detail.

**Table 4. Assessment scales used in Papers I-III (Norwegian versions: Appendix)**

	<b>What does the tool measure?</b>	<b>Tool characteristics and psychometric properties</b>
<b>MMSE</b>	Staging of cognitive impairment based on scores in 11 domains (registration, orientation to time and place, short-term recall, attention, calculation, long-term recall, naming, repetition, comprehension (verbal and written), writing, and visuospatial construction), questionnaire administered directly to the patient by the researchers	30 items assess cognitive function to yield a sum score which differentiates level of impairment from severe (0-10), moderate (11-20), mild (21-25), to no impairment (26-30). <sup>166,167</sup> MMSE is widely used as a screening tool, with good reliability and validity. <sup>167,168</sup>
<b>MOBID-2 Pain Scale</b>	Pain from the musculoskeletal system during standardized, guided movement (part 1, current), and internal organs, head and skin (part 2, in the last days/week), proxy rated by interview with NH staff	Assessment of pain intensity in dementia inferred by observable pain behaviours; pain from the musculoskeletal system (part 1) and pain from internal organs, head, and skin (part 2). <sup>169,170</sup> Each item is rated on a horizontal scale from 0 (no pain) to 10 (worst pain imaginable). Yields a final assessment of total pain (range 0-10). Excellent reliability and validity, good responsiveness. <sup>171</sup> Total pain $\geq 3$ was regarded as moderate to severe pain.
<b>CSDD</b>	Depressive symptoms in people with dementia in 5 domains (mood-related signs, behavioural disturbance, physical signs, cyclic function, and ideational disturbance) in the last week, proxy rated by interview with NH staff	19 items with each symptom score rated from 0 (not present) to 2 (severe). <sup>172</sup> Satisfactory interrater reliability and validity in the elderly population. <sup>173</sup> Sum score $\geq 8$ defined as depression. <sup>54</sup>
<b>NPI-NH</b>	The frequency and severity of 12 neuropsychiatric items in dementia (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, loss of inhibition, irritability/lability, aberrant motor behaviours, sleep and appetite and eating disturbances), proxy rated by interview with NH staff	The product of frequency (0-4) x severity (1-3) yields a composite score per item from 0 (not present) to 12 (most frequent and severe symptoms), with a cut-off value of $\geq 4$ for clinically significant symptoms, total sum score 0-144. <sup>30</sup> The Norwegian version has shown good reliability and validity. <sup>31</sup>
<b>Actigraphy</b>	A wrist-worn microelectromechanical system accelerometer (Philips Actiwatch Spectrum PLUS/PRO) provides objective recording of interval duration and intensity of movement, to yield 24-hour activity and rest patterns for 7-14 days	Total activity counts per day (Total AC) and mean intensity of activity per minute (AC/min) for daily 12-hour intervals (09:00-21:00) were extracted from the Respirationics Actiware 5 software, and mean activity counts for Total AC and AC/min were calculated for 7-day periods with at least 5 valid days of recording per week. <sup>174,175</sup>

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

---

The **Mini-Mental State Examination (MMSE)** was used as a screening tool to group patients according to cognitive state. Although the instrument has shown good reliability and validity as a screening tool, the MMSE alone cannot be used to diagnose dementia.<sup>176</sup> Several important limitations should be acknowledged. As it is administered directly to the patient, it is sensitive to daily fluctuations in mood or motivation to respond. Cognitive function may be underestimated in people with dementia and/or symptoms of depression or apathy, who may lack motivation to respond. The MMSE has also been criticized for underestimating mild cognitive impairment, particularly in people with high education in whom the MMSE is known to overestimate cognitive function.<sup>176</sup> Similarly, low education is associated with lower MMSE scores and cognitive function may be underestimated in people with low education. In addition to education level, the MMSE may also be affected by age and gender. However, as a screening tool the MMSE has shown sufficient sensitivity and specificity.<sup>167,176,177</sup> We have chosen to differentiate between the following four stages of dementia; no cognitive impairment (MMSE 26-30), mild cognitive impairment (MMSE 21-24), moderate cognitive impairment (MMSE 11-20), and severe cognitive impairment (MMSE 0-10). These cut-off values have shown substantial agreement with the Clinical Dementia Rating scale, another widely used assessment tool, for identifying people with mild, moderate, and severe dementia.<sup>167</sup>

Depressive symptoms were assessed using the **Cornell Scale for Depression in Dementia (CSDD)**, which has been validated and used in clinical studies including people with and without dementia.<sup>54</sup> Each of the 19 items is rated from zero (no symptom) to two (severe symptoms), or *a* (not possible to evaluate). The CSDD yields a sum score of between zero (no depression) and 38 (most severe depression), and has shown optimal sensitivity for depression at scores  $\geq 6$  (sensitivity 0.91, specificity 0.73), while the specificity is optimal using  $\geq 8$  as a cut-off for depression (sensitivity 0.78, specificity 0.84) as summarized in a recent systematic review and meta-analysis.<sup>54</sup> The factor structure of the CSDD scale was recently investigated by Barca et al., in a sample of 1682 people with mild to severe dementia recruited from nursing homes and memory clinics. Five symptoms clusters were identified: mood; physical; cyclic; retardation; and behavioural symptoms. The mood factor included



the items suicide, pessimism, poor self-esteem, sadness, mood-congruent delusions, and multiple physical complaints.<sup>178</sup> Although previous studies have found somewhat varying factor structures, the mood factor as well as the cyclic factor that was found in this study are quite stable across previous studies, as reviewed by the authors.<sup>178</sup> The physical factor included the symptoms weight loss and appetite loss; the cyclic factor included the symptoms multiple awakenings during sleep and difficulty falling asleep; the retardation factor included the items loss of interest, lack of joy, lack of energy, retardation, and agitation; and finally the behaviour factor included the items diurnal variation, anxiety, and irritability.<sup>178</sup> Interestingly, the authors found that all factors except the mood and cyclic factors increase in severity as dementia progresses, suggesting a potential overlap between other CSDD items and dementia symptoms.<sup>178</sup>

We assessed pain using the **Mobilisation-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale**, a two-part staff-administered behavioural instrument to assess pain in older persons with advanced dementia.<sup>170,171</sup> The evaluation of inferred pain intensity is based on the patient's pain behaviours during standardised, guided movements of different body parts to assess pain from the musculoskeletal system (Part 1), and pain behaviours related to internal organs, head and skin are registered on pain drawings and monitored over time (Part 2).<sup>171</sup> Excellent interrater and test-retest reliability, internal consistency and validity have been reported.<sup>170</sup> The tool has also demonstrated responsiveness to treatment, as it is able to assess change in the total score (range 0-10) after pain treatment has been initiated.<sup>171</sup>

The **Neuropsychiatric Inventory – Nursing Home version (NPI-NH)** was used to assess the total presence of neuropsychiatric symptoms, calculated as the sum of individual symptom scores (frequency x intensity).<sup>30</sup> In addition, the NPI-NH depression item was used as a surrogate measure for depression in order to investigate whether the effects that were found using the CSDD as an outcome measure could be replicated with a different assessment scale.<sup>179</sup> The factor structure of the NPI-NH items has been investigated by several authors, and the depression

item has been found to cluster with symptoms such as anxiety, night-time behavioural disturbances, eating and appetite disturbances.<sup>180-183</sup> Results are somewhat conflicting as to whether apathy should be considered as part of a mood cluster in dementia, or as part of a separate symptom cluster.<sup>183</sup> Differences between the samples, including dementia severity, may explain some of the variability.

Daytime activity was assessed in a subgroup of patients included in the DEP.PAIN.DEM trial, using **wrist actigraphy**. The actigraphs contain accelerometers that record information digitally on intensity and length of movement in active periods. They were worn continuously on the patient's dominant wrist during recording. Actigraphy has been shown to provide a reliable and valid measure of activity.<sup>174,175</sup> Total activity was recorded for 24-hour intervals. To assess daytime activity, total activity per day and mean intensity of activity per minute per day from 09:00 to 21:00 was extracted from the Philips Respironics Actiware 6.0.9 software.

Daily scheduled use of analgesic, antidepressant, or psychotropic drugs was assessed by extracting current prescriptions from the patients' medical records, and classifying each drug according to the **Anatomical Therapeutic Chemical (ATC) system** as shown in Table 5.

**Table 5. Classification of analgesic and psychotropic drugs**

<b>Classification</b>	<b>ATC code</b>	<b>Drug class</b>
Analgesics	M01A	Systemic nonsteroidal anti-inflammatory drugs
	N02	Systemic analgesics
Psychotropic drugs	N03A	Antiepileptic drugs
	N05A	Antipsychotic drugs
	N05B	Anxiolytic drugs
	N05C	Hypnotic/sedative drugs
	N06A	Antidepressant drugs
	N06D	Anti-dementia drugs

ATC; Anatomical Therapeutic Chemical classification system

Use of anticholinergic drugs was assessed using the **Anticholinergic Cognitive Burden (ACB) scale**.<sup>184,185</sup> Each prescribed drug with mild, moderate, and strong anticholinergic properties was assigned 1, 2, and 3 points, respectively, and total ACB was calculated as the sum score of all prescribed anticholinergic drugs.

## **3.3 Paper I**

### **3.3.1 Design**

This was a prospective cohort study including observational data from two independent multicentre studies in nursing homes from 6 counties of Norway; the REDIC (Resource Use and Disease Course in Dementia) trial and the COSMOS (Communication, Systematic pain assessment and treatment, Medication review, Organised activities, and Safety) trial control group.

### **3.3.2 The REDIC study**

#### **Design**

The REDIC (Resource Use and Disease Course in Dementia) trial was a prospective observational study (2012-2017) which included four different cohorts.<sup>13</sup> One cohort consisted of nursing home patients who were followed from admittance to long-term nursing home care (REDIC-NH). The patients were assessed at baseline (within four weeks after admittance) and at 6-month intervals for a total follow-up period of three years. The study was administrated by the Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, and was initiated by the Norwegian Directorate of Health, which also provided funding for the data collection.

#### **Setting and participants**

In total, 182 units from 47 nursing homes in four counties of Norway were included (Hedmark, Hordaland, Nord-Trøndelag, and Oppland), and 696 patients joined the study from January 2012 to June 2014. Eligible patients were  $\geq 65$  years, or younger if they had a diagnosis of dementia, and newly admitted to a nursing home with expected stay  $>4$  weeks. Patients with life expectancy  $<6$  weeks were ineligible for inclusion.

## **Assessments**

The assessments that were used in this thesis were conducted at baseline and after 6 months, and included cognition (MMSE), pain (MOBID-2), depression (CSDD), neuropsychiatric symptoms (NPI-NH), and use of analgesic and antidepressant drugs. Data were collected through structured interviews with the nursing home patients and their caregivers. Assessments were conducted by the nursing home staff after a two-day training program led by 10 research nurses who supervised data collection and provided support as needed. The research nurses completed a five-day training program to qualify them for educating and supervising the data collectors. Demographic information and prescribed drugs were collected through a review of the patients' medical records.

## **Ethics**

Verbal and written informed consent was obtained from the patients if they were deemed to have medical decision-making capacity. In those with reduced capacity to give consent, written consent was obtained from a legally authorised representative in accordance with ethics committee requirements and current Norwegian legislation. The trial was approved by the Regional Committee for Medical and Health Research Ethics (2011/1738) and registered at ClinicalTrials.gov (NCT01920100).

## **Contributions**

Access to data was granted by Professor Geir Selbæk, Research Director, the Norwegian National Advisory Unit on Ageing and Health. The candidate did not contribute to the data collection.

### **3.3.3 The COSMOS study**

#### **Design**

The COSMOS (Communication, Systematic pain assessment and treatment, Medication review, Organised activities, and Safety) study was a multicentre, cluster randomised and controlled effectiveness-implementation hybrid trial (2013-2016)

which included nursing home patients living in the included nursing home unit (cluster) and randomised clusters to either a complex intervention for 4 months or usual care.<sup>186</sup> The patients were assessed at baseline and after 4 and 9 months. The study was administered by the Centre for Elderly and Nursing Home Medicine, University of Bergen, and was funded by the Research Council of Norway (222113).

### **Setting and participants**

In total, 67 units from 33 nursing homes in three counties of Norway were included (Akershus, Hordaland, and Østfold) from August 2014 to December 2015. Eligible participants were  $\geq 65$  years and had been living in the participating ward for at least 4 weeks. Patients with life expectancy  $\leq 6$  months or schizophrenia were ineligible for inclusion. 36 units with 394 residents were cluster randomised to receive the intervention, and 31 units with 329 residents were allocated to the control condition. Of these, 297 and 248 participants, respectively, received the allocated intervention.

### **Intervention**

The units were randomised to receive a multicomponent intervention that consisted of staff education and implementation of structured, evidence-based efforts to increase 1) communication between staff, patient, and relatives to promote advance care planning; 2) systematic assessment and treatment of pain; 3) medication review; 4) meaningful activity; 5) patient safety. Units that were randomised to the control group did not receive any intervention during the follow-up period, but followed a waiting-list strategy with staff education offered after completion of the trial. However, all staff received training related to use of the assessment instruments. This thesis only uses data from the 248 participants who contributed to clinical assessments in the control group.

### **Assessments**

The assessments that were used in this thesis were obtained from the control group only, and were conducted at baseline and after 4 months. Assessments included cognition (MMSE), pain (MOBID-2), depression (CSDD), neuropsychiatric

---

symptoms (NPI-NH), and use of analgesic and antidepressant drugs. Data were collected through structured interviews with the nursing home patients and their primary caregivers. Prior to participation, the proxy raters received a half-day specific training program including the relevant assessment scales. Assessments were conducted by research assistants who had completed a two-day training program to qualify them for collecting data. Demographic information and prescribed drugs were collected through a review of the patients' medical records.

### **Ethics**

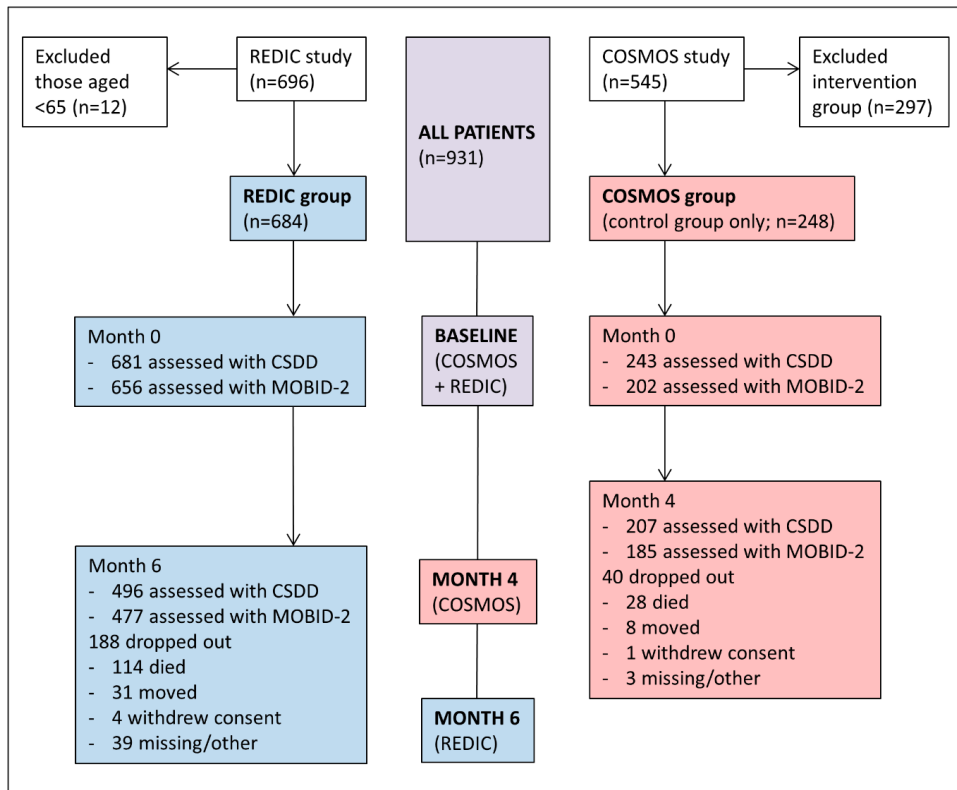
Verbal and written informed consent was obtained from the patients if they were deemed to have medical decision-making capacity. In those with reduced capacity to give consent, written consent was obtained from a legally authorised representative in accordance with ethics committee requirements and current Norwegian legislation. The trial was approved by the Regional Committee for Medical and Health Research Ethics (2013/1765) and registered at ClinicalTrials.gov (NCT02238652).

### **Contributions**

Access to data was granted by Professor Bettina Husebø. The candidate made minor contributions to the planning of the trial, and participated in obtaining informed consent as well as the baseline data collection in the Bergen region, approximately 4 weeks' workload in total.

### **3.3.4 Trial profile**

The database for Paper I included participants from the REDIC and COSMOS trials, aged  $\geq 65$  years, in whom pain and depression had been assessed prospectively without applying any trial intervention (Figure 2).



**Figure 2. Trial profile Paper I.**

COSMOS; Communication, Systematic pain assessment and treatment, Medication review, Organised activities, and Safety, CSDD; Cornell Scale for Depression in Dementia, MOBID-2; Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, REDIC; Resource Use and Disease Course in Dementia

### 3.3.5 Outcome variables

The primary outcomes were the association between pain (MOBID-2) and change in depressive symptoms (CSDD), and the association between depressive symptoms (CSDD) and change in pain (MOBID-2). Furthermore, we investigated whether the observed associations were affected by cognitive state (MMSE), and use of analgesic (M01A/N02) or antidepressant (N06A) drugs. In order to investigate whether the associations were replicated using a different depression assessment scale, the NPI-NH depression item was used as a secondary outcome measure.

---

### 3.3.6 Statistics

Baseline characteristics were described with mean and standard deviation (SD) for continuous variables and with number of participants and percentages of sample size for categorical variables. In order to assess whether the REDIC and COSMOS groups were different at baseline, we used the independent samples *t*-test for normally distributed continuous variables, Mann-Whitney *U*-test for non-normal distributed continuous variables, and Pearson  $\chi^2$ -test for categorical variables.

The unadjusted odds ratio (OR) for depression among participants with moderate to severe pain was calculated at baseline. Linear regression models were fitted to analyse the prospective association between pain at baseline and depression at follow-up, and vice versa, adjusted for depression, pain, age, sex, and cognitive function at baseline. To account for intra-cluster correlation at the nursing home level, we used robust estimators for variance.

To explore whether increasing pain was associated with increasing depression, and vice versa, we used linear mixed effect models with restricted maximum likelihood estimation. We conducted several analyses for the outcome variables where we included fixed effects for MOBID-2, CSDD, time, antidepressant use, and analgesic use (time-varying covariates), and MMSE, age, and sex (time-constant variables). Associations at different stages of cognitive functioning were assessed by stratifying those with no/questionable, mild, moderate, and severe dementia according to MMSE.<sup>167</sup> To account for intra-cluster correlation, the models were fitted with random intercept for both nursing home and patient-level effects. We included random slope for MOBID-2 and CSDD at patient-level, thus allowing the effects of these covariates to vary between patients. The covariance structures were specified using an independent model for both patients and nursing homes. The regression coefficients for the time-varying covariates can be interpreted as a between-patients effect and/or a within-patient effect. In order to explore the contributions of between-patients effects and within-patients effects on the primary outcomes, we included both within and between effects in the same model. Mixed model analyses were also



conducted using NPI-depression as a dependent variable, with MOBID-2, time, MMSE, age, and sex as independent variables, to explore whether any associations obtained using the CSDD scale were replicated. We regarded  $p < 0.05$  as statistically significant. All analyses were conducted with Stata/IC version 14 (StataCorp LP, College Station, TX, USA).

## **3.4 Papers II-III**

### **3.4.1 Design**

These papers present the primary and secondary results from the randomised controlled trial DEP.PAIN.DEM (Efficacy of pain treatment on depression in people with dementia).

### **3.4.2 The DEP.PAIN.DEM trial**

DEP.PAIN.DEM was a multicentre, randomised, placebo-controlled trial (2014-2016) including nursing home patients with advanced dementia and depression. Participants were prescribed an individual increase in analgesic treatment (paracetamol or buprenorphine), and randomised to receive either active treatment or identical, inert placebo for 13 weeks with assessments at baseline, 6 and 13 weeks. The trial was administered by the Centre for Elderly and Nursing Home Medicine, University of Bergen, and was funded by the Research Council of Norway (221951).

#### **Setting and participants**

In total, 162 nursing home patients were included from 47 nursing homes in five counties of Norway (Akershus, Hordaland, Møre og Romsdal, Oslo, Rogaland). Eligible participants were 60 years or older, with moderate to severe dementia according to DSM-5 (MMSE  $\leq 20$ ) and depression (CSDD  $\geq 8$ ) of at least 3 weeks' duration. Exclusion criteria were: cognitive impairment related to other diagnoses than Alzheimer's disease, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, or mixed dementia; life expectancy  $< 6$  months; severe pain (MOBID-2 pain score  $\geq 8$ ), severe aggression (with NPI-NH aggression item  $\geq 8$ ); suicide risk;

---

severe hepatic or renal insufficiency; anaemia (haemoglobin <8.5 mmol/L in men, <7.5 mmol/L in women); uncontrolled epilepsy; severe disease that could interfere with study participation; contraindication or clinically significant drug interaction to the assigned study treatment; and scheduled prescriptions for any opioid analgesic other than or exceeding buprenorphine 5 µg/hour. A drug interaction analysis was conducted by a pharmacist (the candidate), and potential drug-drug and drug-disease interactions were discussed with the nursing home physician who had the final responsibility for considering the appropriateness of treatment, prescribing the study drug, and making clinical decisions in the case of any adverse events. Study treatment was not prescribed to individuals in whom pain was considered likely to be caused by an immediately treatable underlying condition, such as cystitis.

### **Randomisation and blinding**

The trial was double-blinded, and participants were randomly allocated to each arm in a 1:1 ratio according to computer-generated random numbers in blocks of 10 (paracetamol) and 12 (buprenorphine) with no stratification factors. Statisticians generated and sent the randomisation lists directly to the production and packing facilities without researcher involvement. Paracetamol and identical, inert placebo tablets were purchased from Kragerø Tablettproduksjon AS, Norway. Mundipharma Research Limited, UK provided buprenorphine TDS and identical, inert placebo. The patients, carers, clinicians, pharmacy, researchers, and study statistician were masked to group identity until completion of the protocol.

### **Intervention**

Patients were prescribed analgesic treatment according to the stepwise protocol for treating pain (Table 6). All participants continued their usual medical treatment after inclusion in the study (including any regular or “as needed” (PRN) analgesic). The use of PRN analgesics was allowed and monitored during the study, ensuring that all patients received adequate pain treatment irrespective of group allocation. Ongoing treatment with antidepressants, other psychotropic drugs, and regular analgesics was allowed if the dose had remained stable for 4 weeks prior to study inclusion.

Clinicians were advised to keep doses of psychotropic and analgesic drugs unchanged during the study period if possible. If lasting changes were made to regular analgesic treatment or antidepressants, the patient was withdrawn from the study.

**Table 6. Stepwise protocol for treating pain.**

Step	Regular analgesic treatment	Study treatment	Dose
1	No analgesic (1a) or paracetamol $\leq 1$ g/day (1b).	Paracetamol tablets	Max. 3 g/day
		Placebo tablets	Inert placebo
2	Non-opioid analgesic (paracetamol $> 1$ g/day, and/or NSAID), or no analgesic, but with difficulty swallowing tablets (2a), or buprenorphine 5 $\mu$ g/hour (2b).	Buprenorphine TDS	5 $\mu$ g/hour (max. 10 $\mu$ g/hour in 2b)
		Placebo TDS	Inert placebo

NSAID; nonsteroidal anti-inflammatory drug except low-dose acetylsalicylic acid, TDS; transdermal system.

### Assessments

Assessments of depression (CSDD), pain (MOBID-2), neuropsychiatric symptoms (NPI-NH), and use of analgesic, antidepressant and psychotropic drugs were made at baseline and after 6 and 13 weeks. Additionally, cognition was assessed at baseline and after 13 weeks, and actigraphy recordings were obtained from a subgroup of patients for 14 days at baseline (1 week prior to and 1 week after initiation of study treatment), and for 7 days during week 13 (the last week of treatment).

Adverse events were recorded as reported by nursing home staff, who were provided with a comprehensive list of known adverse effects of the study treatment based on information from the Summary of Product Characteristics, and instructed to contact the researchers by phone immediately if an adverse event was suspected. The researchers were available by phone 24 hours a day for the duration of the trial. In addition, the raters were asked specifically about whether they had observed any suspected adverse event during scheduled data collection (week 0, 6, and 13) and spontaneous contacts. Adverse events were registered and grouped according to the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy for system organ classification.<sup>187</sup> All reported adverse events were recorded upon suspicion,

---

regardless of whether or not they were deemed likely to be caused by the study treatment.

Data were collected through structured interviews with the nursing home patients and their primary caregivers. Assessments were conducted by research assistants who had completed a two-day training program to qualify them for collecting data.

Demographic information and prescribed drugs were collected through a review of the patients' medical records.

### **Ethics**

Verbal and written informed consent was obtained from the patients if they were deemed to have medical decision-making capacity. In those with reduced capacity to give consent, written consent was obtained from a legally authorised representative in accordance with ethics committee requirements and current Norwegian legislation.

The trial was approved by the Regional Committee for Medical and Health Research Ethics (2013/1474) and the Norwegian Medicines Agency (EudraCT 2013-002226-23), and registered at ClinicalTrials.gov (NCT02267057). Participants were insured to cover compensation and treatment in the event of drug-related harm.

### **Contributions**

The candidate made major contributions to the planning and conduction of the trial from 2014-2016, in cooperation with fellow Ph.D. Candidate Kjersti Marie Blytt from 2015-2016. The candidates recruited all of the nursing homes, screened the nursing home patients for eligibility, obtained informed consent from all eligible patients and their relatives, and conducted baseline and follow-up assessments in cooperation with the nursing home staff. As a licensed pharmacist, the candidate handled the storage and distribution of study drugs, destruction of unused drugs, and participated in the labelling of study drugs – thereby providing major savings on pharmacy services for the project. In addition, the candidate contributed to the communication with drug manufacturers, the Norwegian Medicines Agency, and the

Regional Committee for Medical and Health Research Ethics (REK-Vest) in order to finalize the necessary approvals.

### **3.4.3 Paper II**

#### **Design**

This paper presents the primary results from the DEP.PAIN.DEM trial, a randomised, multicentre, double-blind placebo-controlled trial to assess the efficacy of analgesic treatment for depressive symptoms in nursing home patients with dementia and depression.

#### **Trial profile**

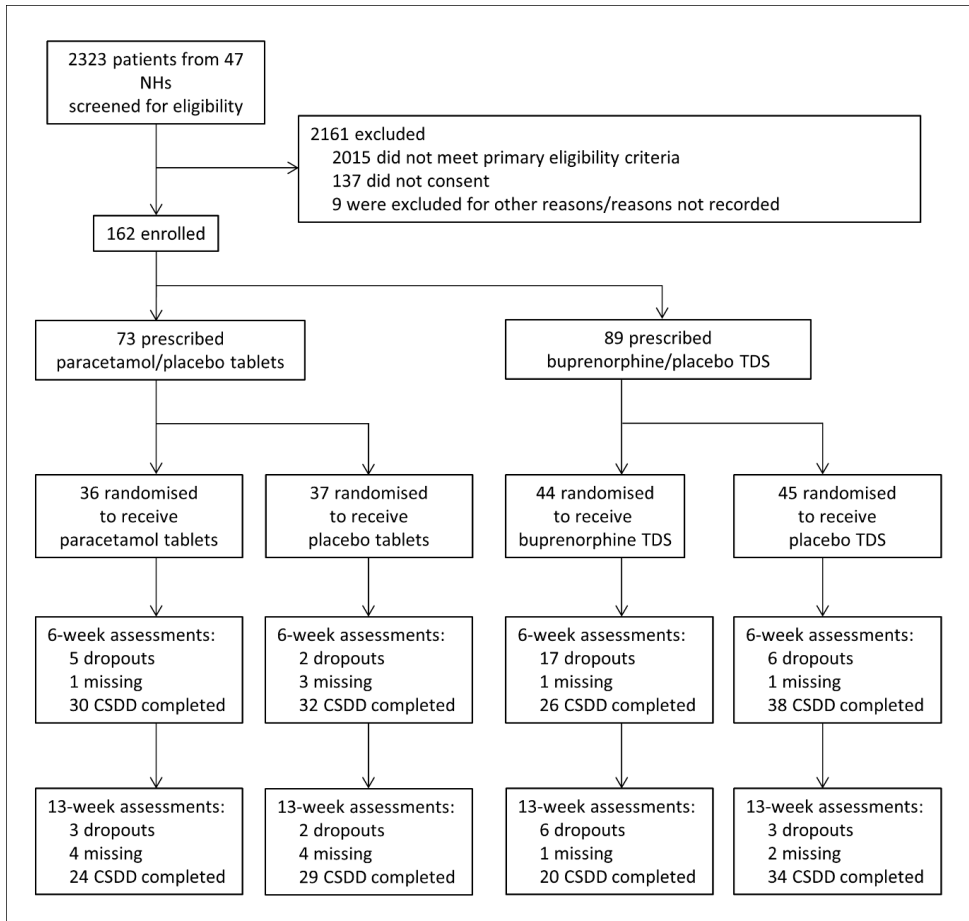
All participants in the DEP.PAIN.DEM trial were included in the database for Paper II (Figure 3). Participants were long-term nursing home patients ( $n=162$ ) aged  $\geq 60$  years with dementia ( $MMSE \leq 20$ ) and depression ( $CSDD \geq 8$ ); for full inclusion and exclusion criteria, see section 3.4.2.

#### **Outcome variables**

The main outcome was treatment effect on change in depression (CSDD) from baseline to 13 weeks. In order to assess whether any change in depression was caused by decreased pain, change in pain (MOBID-2) was a secondary outcome, as well as adverse events and dropouts from treatment.

#### **Statistics**

Baseline characteristics were presented as mean (SD) for continuous variables and number of participants (%) for categorical variables. Treatment effects on both the primary outcome (depression assessed by the CSDD) and the secondary outcome (pain assessed by the MOBID-2 Pain Scale) were assessed separately using linear mixed effects models which incorporated all assessments at baseline, 6, and 13 weeks. We treated time as a categorical variable, and included fixed effects for time, intervention and their interaction in the models. To account for clustering, the models



**Figure 3. Trial profile Paper II**

CSDD; Cornell Scale for Depression in Dementia, TDS; transdermal system

were fitted with random intercepts for nursing home units and individuals. Treatment effects were calculated for active treatment versus placebo, these analyses were repeated with use of other analgesics or antidepressants at baseline as covariates to control for any impact of concomitant drug use. We also conducted pre-planned subgroup analyses for paracetamol tablets compared to placebo tablets, buprenorphine TDS compared to placebo TDS, and to investigate treatment effects stratified for level of cognitive function and for the presence of moderate to severe pain. We regarded  $p < 0.05$  as significant. All statistical analyses were conducted with STATA/IC 14 (Stata Corp LP, College Station, TX, USA).

### **3.4.4 Paper III**

#### **Design**

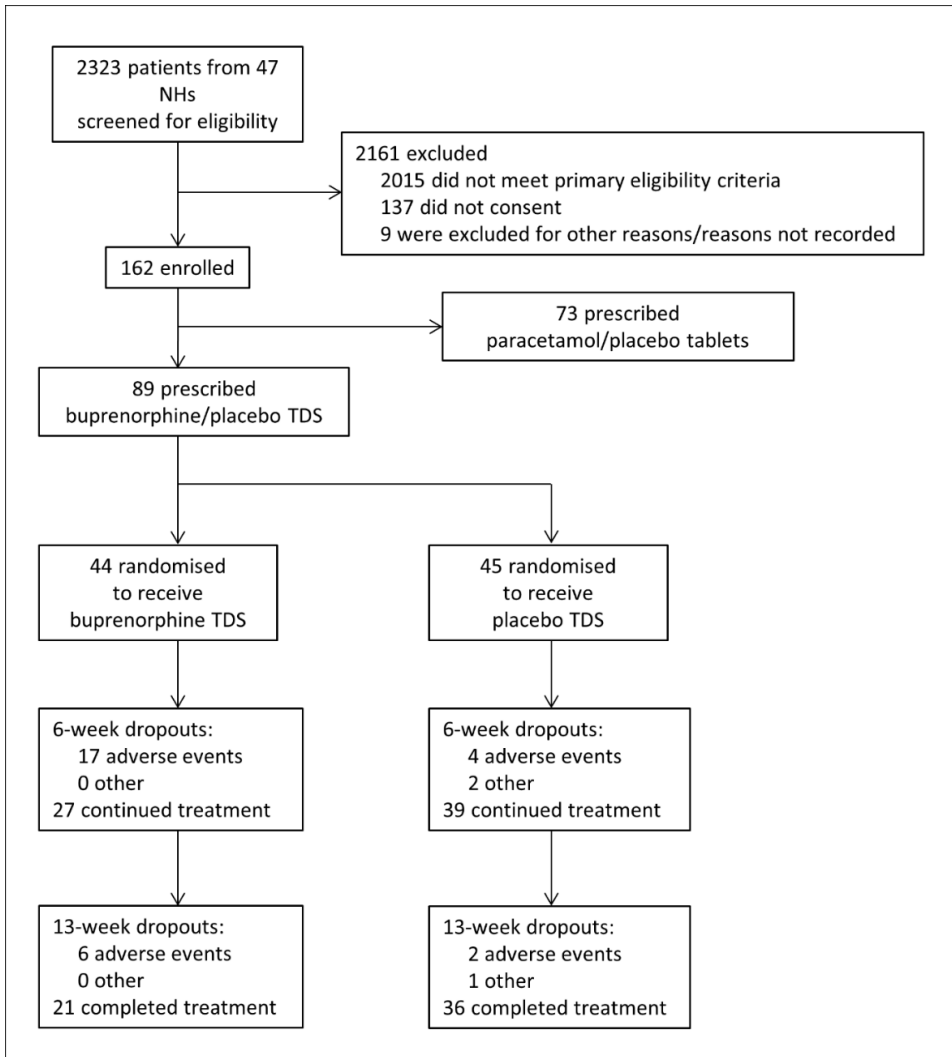
This paper presents secondary analyses from the DEP.PAIN.DEM trial, and is the first randomised, double-blind placebo-controlled trial to assess the tolerability of buprenorphine TDS in people with advanced dementia.

#### **Trial profile**

The 89 participants who were prescribed buprenorphine (active/placebo) in the DEP.PAIN.DEM trial were included in the database for Paper III (Figure 4).

#### **Outcome variables**

The primary outcome was time to discontinuation of active treatment compared to placebo, controlling for cognitive function and concomitant drug use. The secondary outcome was treatment effect on activity during the first week of treatment, measured by continuous actigraphy recording for 7 days before and 7 days after treatment was started. The tolerability of buprenorphine TDS was operationalized by assessing how many participants discontinued treatment due to adverse events (defined as suspected adverse event, clinical deterioration, or death), and how long treatment lasted before such discontinuation. The impact of regularly scheduled drug use (excluding prescriptions administered PRN or “as needed”) on tolerability was assessed, including total number of prescriptions, ACB, use of analgesic drugs, and the individual and total number of prescriptions for psychotropic drugs.



**Figure 4. Trial profile Paper III**

TDS; transdermal system

## Statistics

We used a Cox regression model to determine whether those who were randomised to receive active buprenorphine had a higher risk of discontinuation compared to those who received placebo. These analyses were repeated with age, sex, MOBID-2, CSDD, MMSE, and use of other analgesics or antidepressants at baseline as



covariates. To further assess whether the risk of discontinuation of buprenorphine was modified by drug use, we tested the interaction between the treatment effect and each of the drug variables on discontinuation, both unadjusted and adjusted for age, sex, MOBID-2, CSDD, and MMSE at baseline. To assess immediate changes in activity in the first days of treatment, we used linear mixed effect models for Total AC and AC/min per day using the mean recording from the 7 days before treatment was initiated as baseline. Time was included as a categorical variable, with fixed effects for time, intervention, and their interaction in the models. To account for clustering, the models were fitted with random intercepts for nursing home units and individuals. We regarded  $p < 0.05$  as significant. All statistical analyses were conducted with STATA/IC 14 (Stata Corp LP, College Station, TX, USA).

---

## 4. Main results

### Paper I

Erdal A, Flo E, Selbaek G, Aarsland D, Bergh S, Slettebo DD, Husebo BS.

Associations between pain and depression in nursing home patients at different stages of dementia. *J Affect Disord* 2017;218:8-14.

- Many of the included participants had pain and depression. 40% suffered from moderate to severe pain (MOBID-2 $\geq$ 3) at baseline (343 of 858 assessed), and 38% had depression (347 of 924 assessed).
- Half of those with depression also had pain (19% or 164 of the 856 participants who completed both assessments), and those with pain had increased risk for depression (unadjusted odds ratio 2.35, 95% CI 1.76; 3.12).
- Pain and depression persisted to follow-up in about half of those diagnosed at baseline. Persistent moderate-to-severe pain was found in 22.2% of the sample (137 of the 617 participants who completed both pain assessments), and 20.6% had persistent depression (144 of the 699 participants who completed both depression assessments).
- Those who had more severe pain had significantly more depressive symptoms; a 1-point increase in MOBID-2 pain was associated with a 0.5 increase in CSDD ( $p < 0.001$ ; mixed model with adjustment for time from baseline to follow-up). Similarly, those with more severe depressive symptoms also had significantly more pain; a 1-point increase in CSDD was associated with a 0.1 increase in MOBID-2 pain ( $p < 0.001$ ; mixed model). These associations were not affected by cognitive function (MMSE), and remained unchanged when adjusting for age, sex, and number of analgesics and/or antidepressants.
- This was the first publication to determine that having pain was associated with future worsening of depression, and vice versa, in people with dementia.
- In the COSMOS group, pain intensity at baseline was associated with a significantly higher burden of depressive symptoms at 4-month follow-up (linear regression, RC .41,  $p = 0.026$ ; adjusted for depression at baseline,

---

MMSE, sex, and age), but not in the REDIC group after 6-month follow-up (RC .08,  $p=0.358$ ).

- Those who had more severe depressive symptoms at baseline had significantly more pain at 6-month follow-up in the REDIC group (linear regression, RC .05,  $p=0.008$ ; adjusted for pain at baseline, MMSE, sex, and age). The same association was not significant in the COSMOS group after 4-month follow-up (RC .06,  $p=0.064$ ).
- In the REDIC population, we found a significant within-subject effect of pain on depressive symptoms, i.e. a person who had reduced pain at follow-up had significantly less depressive symptoms at follow-up compared to baseline (mixed model, between-subject coefficient .62,  $p<0.001$ ; within-subject coefficient .23,  $p=0.042$ ). In the COSMOS population, only the between-subject effects were significant ( $p=0.317$  for within-subject effects).
- We did not find that the obtained association between pain and depression can be explained by overlap between pain and CSDD items such as multiple physical complaints, as the association was replicated using the NPI-NH depression item as an alternative outcome in the mixed model analysis; a 1-point increase on the MOBID-2 scale was significantly associated with a .11 increase on the NPI-NH depression subscale ( $p=0.005$ ).

## Paper II

Erdal A, Flo E, Aarsland D, Ballard C, Slettebo DD, Husebo BS. Efficacy and Safety of Analgesic Treatment for Depression in People with Advanced Dementia: Randomised, Multicentre, Double-Blind, Placebo-Controlled Trial (DEP.PAIN.DEM). *Drugs Aging* 2018;35(6):545-558.

- We did not find that depressive symptoms could be ameliorated by treating undiagnosed pain in people with dementia.
- Depressive symptoms remained unchanged in the group that received active treatment (paracetamol/buprenorphine; mean CSDD change -0.66, 95% CI -2.27; -0.94).

- 
- In contrast, the placebo group had a significant improvement in depressive symptoms from baseline to 13 weeks (mean CSDD change -3.30; 95% CI -4.68; -1.92).
  - The estimated effect of active treatment on depressive symptoms from baseline to 13 weeks was therefore significant in favour of placebo, as active treatment (paracetamol/buprenorphine) was associated with a significant increase of 2.64 on the CSDD scale (95% CI 0.55; 4.72,  $p=0.013$ ) relative to placebo.
  - We were unable to detect a significant treatment effect of paracetamol ( $n=73$ ) on depression; active paracetamol was associated with a 1.98 increase in CSDD depression relative to placebo tablets (95% CI -0.79; 4.74).
  - Buprenorphine was associated with a near-significant 3.04 increase in CSDD depression relative to placebo TDS; however, the trial was not sufficiently powered to detect subgroup effects, as reflected by the wide confidence interval (95% CI -0.11; 6.19).
  - Overall, there was no significant change in pain from baseline to 13-week follow-up. In those who received active treatment, mean MOBID-2 change from baseline to 13 weeks was -0.28 (95% CI -0.90; 0.35). The corresponding change in the placebo group was -0.09 (95% CI -0.63; 0.46), to yield a non-significant estimated treatment effect of -0.19 (95% CI -1.02; 0.64).
  - Subgroup analyses show that buprenorphine did not appear to reduce pain; the estimated treatment effect was a non-significant increase in MOBID-2 pain of 0.47 (95% CI -0.77; 1.71) from baseline to 13 weeks. However, paracetamol had a near-significant treatment effect on pain estimated to -0.98 (95% CI -2.00; 0.05) from baseline to 13 weeks, and paracetamol reduced pain significantly by -1.11 (95% CI -2.16; -0.06,  $p=0.037$ ) from week 6 to 13 compared to placebo tablets. Other subgroup analyses did not show significant treatment effects on pain.
  - Of the 162 participants who were enrolled in the trial, 35 were withdrawn due to adverse reactions, deterioration, or death: 25 (31.3%) during active treatment, and 10 (12.2%) in the placebo group.

### Paper III

Erdal A, Flo E, Aarsland D, Ballard C, Slettebo DD, Husebo BS. Tolerability of buprenorphine transdermal system in nursing home patients with advanced dementia: a randomized, placebo-controlled trial (DEP.PAIN.DEM). *Clin Interv Aging* 2018;13:935-46.

- Of 44 participants who received buprenorphine 5 µg/hour, 52.3% (n=23) discontinued treatment due to adverse events compared to 13.3% (6 of 45) in the placebo group (p<0.001). Five participants who received buprenorphine and three who received placebo died during the study period, this difference was not significant (Pearson  $\chi^2$ -test, p=0.439).
- Mean time to discontinuation was 61 days (SD 36) in the buprenorphine group, and 82 days (SD 24) in the placebo group. Within the first 14 days, nine participants (20.5%) discontinued buprenorphine, and two (4.4%) discontinued placebo treatment.
- Adverse events which caused discontinuation of active treatment were most frequently described as exacerbation of neuropsychiatric symptoms, and of the 23 participants who discontinued buprenorphine, adverse events classified as psychiatric and/or neurological symptoms were reported as the cause in 16 (69.6%).
- Sedation/somnolence was the single most frequently reported adverse effect, with nine participants (20.5%) affected in the buprenorphine group and two (4.4%) in the placebo group (p=0.022). Actigraphy recording of daytime activity during the first week of treatment also showed that those who received buprenorphine had a 12.9% decrease in mean daytime activity (Total AC), but this effect was not statistically significant (mixed model; p=0.053).
- However, those who received buprenorphine had significantly reduced daytime activity on the second day of treatment compared to placebo (mixed model; Total AC: -16967, p=0.005). This corresponds to a 21.4% decrease in total daytime activity compared with the mean daytime activity recorded during the week before treatment was started.

- 
- Unadjusted analyses show that those who received buprenorphine had 4.7 times increased risk of discontinuation due to adverse events compared with those who received placebo (Cox proportional hazards model, hazard ratio (HR), 95% CI 1.66; 13.3,  $p=0.004$ ). When adjusted for age, sex, MMSE, MOBID-2 and CSDD at baseline, active treatment was associated with 24.0 times higher risk of discontinuation ( $p=0.006$ ).
  - When testing the interaction effects between active treatment and variables for concomitant drug use on discontinuation risk, we found that only antidepressant drugs were associated with increased risk for adverse events and discontinuation of treatment. Those who used an antidepressant and received buprenorphine ( $n=14$ ) had 21.6 times increased risk of discontinuation compared with those who used an antidepressant and received placebo ( $n=27$ ; unadjusted HR, 95% CI 2.75; 170,  $p=0.003$ ). Adjusting for age, sex, MMSE, MOBID-2, and/or CSDD did not impact the result.
  - In the same analysis, we found that in those who received buprenorphine and did not use an antidepressant ( $n=30$ ) the risk of discontinuation was not significantly increased compared with those who received placebo and did not use an antidepressant ( $n=18$ ; unadjusted HR 1.88, 95% CI 0.63; 5.64,  $p=0.257$ ). This shows that a drug-drug interaction between antidepressants and buprenorphine TDS may have caused the poor tolerability of buprenorphine.

## 5. Discussion

### 5.1 General considerations

This thesis aims to investigate the relationship between pain and depression in people with dementia, and to assess the efficacy and safety of analgesic treatment for depressive symptoms in nursing home patients with advanced dementia and depression. The interrelationship between pain and depression in elderly nursing home patients at all stages of dementia and cognitive impairment was confirmed in the cohort study presented in Paper I.

Although the observational design of Paper I does not allow any conclusion on the direction of causality, this result supports the rationale for and main hypothesis investigated in Paper II, namely that systematic assessment, identification and treatment of undiagnosed pain may ameliorate depressive symptoms in nursing home patients with advanced dementia and depression who are unable to verbally communicate symptoms of pain and discomfort.

Based on previous studies, we anticipated that our results would confirm an association between untreated pain and depressive symptoms in people with dementia, and furthermore that treating pain can reduce depression in this population. However, Paper II presented results from a randomised controlled trial to assess the efficacy of an individual increase in analgesic treatment on depressive symptoms in people with advanced dementia (DEP.PAIN.DEM) and found that, contrary to our initial hypothesis, people who received active analgesic treatment had significantly more persistent depressive symptoms compared to those who received placebo.

The DEP.PAIN.DEM trial was designed in order to minimise the risk of harm to the included participants, and therefore had very stringent inclusion and exclusion criteria. It may seem counter-intuitive that the included participants were not required to have a minimum of untreated pain, and even that participants with severe pain (MOBID-2  $\geq 8$ ) were excluded from the trial. The latter was necessary for several reasons. Firstly, the placebo-controlled design meant that we could not risk untreated

severe pain in those who were randomised to the placebo condition. Secondly, the maximum allowed analgesic dose was low in order to reduce risk of adverse effects, and may have been insufficient to treat severe pain. Importantly, although MOBID-2 pain was not an inclusion criterion, this does not mean that we know for certain that participants with a MOBID-2 score of zero at baseline did not, in fact, have pain. The MOBID-2 score is our best approximation for quantifying pain intensity in this population, but does not equate to the persons' subjective pain experience which remains unknown. This is at the core of the rationale for the DEP.PAIN.DEM trial, which hypothesized that undiagnosed pain may contribute to depressive symptoms in people with moderate to severe dementia.

In Paper III, adverse events reported during treatment with active buprenorphine TDS were investigated. Paper III followed up on preliminary results from Paper II which indicated that those who received active analgesic treatment may have had more persistent depressive symptoms because of psychiatric adverse effects of buprenorphine TDS.

The following discussion aims to provide a critical appraisal of the methodological basis, implications for practice, and external validity of the findings presented in Papers I-III, as well as important ethical considerations in relation to the methods, results, and wider dissemination of the conclusions presented in this thesis.

## **5.2 Discussion of study methods**

### **5.2.1 Paper I: a cohort study**

To investigate the bidirectional associations between pain and depression in people with dementia, we chose a prospective observational study design including two different cohorts of nursing home patients. The two cohorts had different inclusion criteria, which may impact generalisability of the results.

The largest cohort (REDIC sample) consisted of people who were recently admitted to long-term nursing home care. They were younger, relatively fewer women, had



less severe dementia, less pain, less depression and less severe neuropsychiatric symptoms compared to the smaller cohort (COSMOS sample) that was recruited regardless of length of stay. While the latter sample is likely to be representative of the general nursing home population, the former sample may provide findings that are more generalizable to nursing home patients with short lengths of nursing home stay. Despite this limitation, we chose to merge the two cohorts in the main analyses. By this approach, we were able to achieve a more balanced sample in terms of cognitive function as shown in Table 7.

**Table 7. Distribution of cognitive function in Paper I cohorts**

	<b>REDIC</b> (n=623)	<b>COSMOS</b> (n=216)	<b>Total</b> (n=839)
<b>No/questionable dementia</b> (MMSE 26-30)	6.6%	4.2%	6.0%
<b>Mild dementia</b> (MMSE 21-25)	15.2%	9.7%	13.8%
<b>Moderate dementia</b> (MMSE 11-20)	59.2%	41.7%	54.7%
<b>Severe dementia</b> (MMSE 0-10)	18.9%	44.4%	25.5%

COSMOS; Communication, Systematic pain assessment and treatment, Medication review, Organised activities, and Safety, MMSE; Mini-Mental State Examination, REDIC; Resource Use and Disease Course in Dementia

Although the prospective observational design is well suited to illustrate associations between exposure or independent variables and outcome or dependent variables, this design cannot generate conclusive data on causal relationships. We have observed effects within individuals which indicate that pain reduction was associated with reduced depressive symptoms, or similarly that pain exacerbation was associated with increased depressive symptoms. Importantly, these associations must be tested in a randomised controlled trial in order to determine any direction of causality between pain and increased depression, and vice versa.

---

### 5.2.2 Papers II-III: a randomised placebo-controlled trial

To test the hypothesis of causality between pain intensity and depressive symptoms, we used a randomised, double-blind, placebo-controlled trial design. This design has the advantage of controlling the exposure to the independent variable, which in contrast to observational trials can facilitate evidence on causality. The placebo-control has the additional advantage of eliminating many known sources of bias in open-label randomised controlled trials, such as expectation effects, to provide strong evidence for the intervention effects. Randomised, double-blind placebo-controlled trials are therefore regarded as the gold standard for generating evidence on causality.<sup>188</sup>

However, the quality of the evidence is dependent on the strength of the study design. In randomised controlled trials, the aim is to keep all variables except exposure to the intervention balanced between the intervention and control groups in order to isolate the intervention effect as the difference between groups. Therefore, stringent inclusion and exclusion criteria are often applied. This means that the population under study may not be generalizable to the real-world population.<sup>189</sup> Furthermore, the study protocol may differ from real-world clinical decisions in ways that impact generalisability.

In the DEP.PAIN.DEM trial, we were only able to include about 7% of the 2323 nursing home patients who were screened for eligibility. The majority of excluded individuals were ineligible for inclusion due to regular use of opioid analgesics (24% of all screened nursing home patients), because they did not have depression (39%), or did not have dementia (6%). These combined 69% were not in the target group for the intervention, and/or would be unlikely to have any benefit from the intervention on the main outcome (depression). This leaves 24% of the screened population, who were excluded for various reasons of which renal failure, change of placement, severe psychiatric disorder, or short life expectancy/death were most frequent. Note that the reason for exclusion was registered based on the first exclusion criterion that was fulfilled, after which no further assessments were conducted. In order to reduce

unnecessary resource use and patient involvement, MOBID-2 was assessed after the medical record review and interview with the primary caregiver was completed. Therefore, none of the screened individuals were registered as excluded because of severe pain. Only 137 individuals (6% of the 2323 screened; or 46% of the 299 individuals who were otherwise eligible for inclusion) were excluded because they, or most frequently their guardians, declined to participate. Based on these data, the results from the DEP.PAIN.DEM trial should have generalisability to the target population which is nursing home patients with dementia and depression who do not have acknowledged severe pain and do not use opioid analgesics except low-dose buprenorphine TDS.

### **5.2.3 Use of proxy rating scales**

Proxy rating was a prerequisite for obtaining assessments of the relevant outcomes in participants with advanced dementia. This is illustrated by Pautex et al. who found that less than half of people with MMSE  $\leq 6$  were able to comprehend and use any pain assessment scale even after repeated instructions.<sup>94</sup> In the DEP.PAIN.DEM trial, the participants had a mean MMSE score of 7.8, and the subgroup in Article III had a mean score of 7.0. Instead of using a mixture of self-report and proxy-rated assessment scales, we decided to use the same assessment scales in all participants regardless of cognitive state in order to facilitate between-group comparisons. The same procedure has been used in several comparable trials.<sup>67,74</sup> However, the use of proxy reports for the assessment of subjective outcomes such as pain and depression increases the risk of bias because the response will be affected by the rater's own perception, understanding, and judgment.<sup>190</sup> Although proxy rating is the best available method to gather information about these symptoms in people with advanced dementia, it is important to keep in mind that proxy ratings of pain and depression are assumed to have only low to moderate agreement with self-reported symptom intensity.<sup>190</sup> Meanwhile, self-reported pain and depression in people with dementia are generally biased toward lower symptom intensity because of decreased awareness of and understanding of symptoms, and therefore may not be the

---

appropriate “gold standard” even in people with mild to moderate dementia who are still able to describe their symptoms.<sup>190</sup>

When family caregivers are asked to rate the health or wellbeing of people with dementia, they generally report higher levels of suffering compared to the persons’ self-rated symptoms.<sup>191</sup> Caregivers with poor psychological well-being and health status report more suffering, with a higher discrepancy between proxy-rated and self-rated symptoms.<sup>191</sup> In caregivers who are asked to rate patients’ health-related quality of life, their own self-rated quality of life is significantly associated with their response on behalf of the patient.<sup>192</sup> Caregivers with pain report higher proxy-rated pain intensity in people with dementia, and caregivers with depression tend to report that patients suffer from higher levels of symptoms or disability.<sup>193</sup> While similar characteristics of the formal caregivers who provided observations are likely to be associated with the rated symptom intensity, we have not attempted to assess or control for pain or depression in the proxy raters.

However, by using the same proxy-rated scales in all included participants, we are able to collect the same data for all participants, regardless of dementia severity, and control for the effects of dementia progression in our data. Furthermore, whenever possible, we attempted to use the same proxy rater at each assessment of the same participant in order to minimise the effects of between-rater variability. The screening tools that were used to detect depression, pain and dementia were not intended for diagnostic use, and no universally accepted cut-off values exist for the CSDD, MOBID-2, or MMSE scales.

### **Diagnosis and course of depression: impact of dementia severity**

The diagnostic accuracy of the CSDD scale at different cut-off values has recently been reviewed in a meta-analysis by Goodarzi et al.<sup>54</sup> We intended to include people with moderate-to-severe depressive symptoms, and therefore did not apply the CSDD cut-off scores that are intended to diagnose major depressive disorder, which are typically higher. To ensure that the included participants had persistent depressive symptoms of at least 4 weeks’ duration, depression was assessed at screening and re-

assessed at baseline. To reduce false positives at screening, the inclusion criterion was chosen as the cut-off with optimal specificity ( $\geq 8$ ).<sup>54</sup> As depressive symptoms often fluctuate over time, we used the cut-off with optimal sensitivity ( $\geq 6$ ) at baseline as a criterion for persistent depression.<sup>54</sup> While this does not imply that all participants had a depressive disorder, they did have sufficient depressive symptoms to allow us to detect change in symptom severity during treatment, as shown in the sample size analysis for the primary outcome of the DEP.PAIN.DEM trial.

The accuracy of the CSDD scale may be affected by dementia severity. Studies that have assessed the psychometric properties of the CSDD scale have primarily included people with mild to moderate dementia.<sup>54</sup> In a longitudinal study with 74-month follow up of 1158 nursing home residents, dementia severity was associated with higher CSDD scores in both mood and non-mood items.<sup>53</sup> This corresponds to results from a factor analysis of the CSDD scale which found that the total score was significantly higher in people with severe dementia compared to those who had mild or moderate dementia.<sup>178</sup> Several items rated by the CSDD scale may overlap with dementia symptoms, such as apathy or agitation, and therefore increase in severity as dementia progresses. Barca et al. examined the five-factor structure of the CSDD scale (symptom subscales: mood; physical; cyclic; retardation; behaviour) at different stages of dementia, and found that mood and cyclic symptoms were not significantly associated with dementia severity, while scores for physical and behavioural symptoms and retardation were significantly higher in advanced dementia.<sup>178</sup> This suggests that the latter three factors may not precisely assess depression in severe dementia due to overlap with symptoms of dementia, while mood and cyclic function may persist as core symptoms of depression in advanced dementia.<sup>178</sup>

Although symptoms of dementia and depression as assessed by the CSDD scale overlap and may be difficult to distinguish, the follow-up period of the DEP.PAIN.DEM trial (13 weeks) is likely too short to expect dementia progression to influence our results significantly. This is supported by preliminary analyses of change in cognitive function (MMSE) from baseline to follow-up, which do not show significant change between or within groups. Furthermore, any effect of dementia

---

progression on the course of CSDD depressive symptoms should be balanced between active treatment and placebo.

### **The Neuropsychiatric Inventory – Nursing Home Version**

Although the NPI-NH was not used as a primary outcome, the use of the depression subscale of the NPI-NH as an alternative measure of depression is supported by several validity studies which have shown significant correlation with NPI-NH depression and other rating scales for depression in dementia.<sup>30,179,194</sup> Selbaek et al. found a Spearman's correlation coefficient of 0.60 between the Norwegian translations of the NPI-NH depression item and the CSDD scale ( $p < 0.01$ ).<sup>195</sup> Interestingly, several studies that have investigated the factor structure of the NPI-NH scale have found that apathy does not cluster with affective symptoms, suggesting that apathy may represent a separate syndrome from depression. Other symptoms that are included in the CSDD scale but may not be clustered with NPI-NH affective symptoms include agitation, irritability, and appetite and eating disturbances.<sup>183</sup> However, studies of the NPI-NH factor structure have found varying results, and items that have been clustered with depression in some studies but not others include apathy, anxiety, night-time behaviours and appetite and eating disorders.<sup>180,181</sup>

### **Assessment of pain: the MOBID-2 Pain Scale**

Many assessment scales have been developed to diagnose pain in people with dementia, but the extent to which the different scales have been translated, tested and validated across different clinical settings varies. Current expert recommendations highlight the need to incorporate the following three elements in order to detect and assess pain in people with dementia: facial expressions of pain; behavioural changes or vocalization related to pain; and observation over time, particularly in relation to movement or routines such as daily care.<sup>151</sup> The MOBID-2 Pain Scale includes detailed assessments of all three elements (see Appendix). MOBID-2 has shown excellent interrater and test-retest reliability.<sup>171</sup> In a recent systematic review of pain assessment scales for people with dementia, MOBID-2 was rated among the highest for internal consistency.<sup>196</sup> The tool has also demonstrated responsiveness to change,

as the total pain intensity score was significantly reduced after analgesic treatment.<sup>171</sup> While no single pain assessment tool has been universally recommended, the MOBID-2 Pain Scale has been sufficiently tested and validated to serve as the best-available instrument to assess pain intensity in the current setting, that is, people with dementia residing in long-term nursing home care in Norway.<sup>196</sup>

The MOBID-2 scale therefore represents our best available approximation to the pain intensity experienced by people with advanced dementia who are unable to communicate their symptoms verbally, but no objective standard exists. Furthermore, the optimal cut-points for classifying total pain on the 11-point scale have not been determined. Even for self-reported pain, there is debate as to which cut-points on an 11-point scale can be used to accurately diagnose mild, moderate, or severe pain in different populations.<sup>197,198</sup> Patient characteristics have been found to affect the optimal cut-points. One such trait is catastrophizing, which can be defined as the tendency to worry about the worst possible outcome from a situation.<sup>199</sup> In patients with low catastrophizing tendency, pain scores of  $\leq 3$  correspond to mild interference of pain with functioning, while for patients with high catastrophizing, a cut-point of  $\leq 5$  more accurately reflects mild pain.<sup>200</sup>

Traits in both the proxy rater and the patient are likely to affect the obtained MOBID-2 pain score. Although a cut-point of MOBID-2  $\geq 3$  for clinically relevant pain has been established, the optimal cut-points for mild, moderate, and severe pain intensity have not yet been investigated.<sup>171</sup> While uncertainty remains as to the reliability and validity of diagnosing different levels of pain intensity based on cut-points on the MOBID-2 Pain Scale, the current evidence-base shows satisfactory psychometric properties with regard to monitoring of change in pain intensity.<sup>171</sup> Furthermore, we have controlled for the impact of interrater variability by ensuring that the same rater conducted follow-up assessments whenever possible.

### **Dementia diagnosis and staging of cognitive impairment**

The prevalence of undiagnosed dementia is high in nursing home patients.<sup>201,202</sup> In order to include people with dementia who had not received a diagnosis, we used the

---

MMSE scale to detect individuals with undiagnosed cognitive impairment and to perform a screening of cognitive function. In compliance with DSM-5 criteria, we excluded those with a history of any other condition which may explain the observed cognitive impairment, such as developmental disorders, traumatic head injury, or chronic alcohol abuse. No additional assessments were made in order to diagnose dementia subtypes. In the late stages of dementia, it can be very difficult to distinguish between different types of dementia.<sup>203</sup> Although the protocol was amended to include plans for data collection that would allow making a diagnosis of the most likely dementia type, we were unable to complete the planned interviews with the patients' relatives because of the total workload of the ongoing project. In addition, not all participants had a close relative who could have provided information about the debut and characteristics of cognitive symptoms. Based on previous studies, we assume that most participants had mixed pathology with Alzheimer's disease and vascular lesions.<sup>204</sup> It is unlikely that stratification on dementia subtype would yield information on differential efficacy or tolerability of treatment, given the sample size obtained for the DEP.PAIN.DEM trial.

While the MMSE scale is not diagnostic and poorly identifies mild cognitive impairment, it has shown high accuracy as a screening tool for moderate to severe cognitive impairment related to dementia, with good interrater and internal reliability.<sup>167,205</sup>

However, the MMSE scale has poor responsiveness to change, particularly during short follow-up periods, and therefore may not be sensitive to treatment effects.<sup>205</sup> Learning effects upon repeated assessments may cause bias, particularly when the intervals between testing are short. Although the MMSE scale was included in the DEP.PAIN.DEM protocol as a secondary outcome, the 13-week follow-up is probably too short to expect any significant change in cognitive function, and therefore any treatment effect.



## **5.2.4 Sources of bias**

### **Hawthorne effects**

The Hawthorne effect was originally described in a factory setting, where it became apparent that workers increased their productivity because of the awareness of being studied – rather than as a result of an intervention aimed towards changing their behaviour.<sup>206</sup> In a wider sense, the Hawthorne effect may be used to describe improvement that is observed because the research subjects change their behaviour as a result of their participation in trial procedures, and not because of the efficacy of an intervention on an outcome.<sup>206</sup> In the nursing home setting, with the use of proxy raters, it can be argued that a Hawthorne effect plays a part when a similar improvement is observed in the control and intervention groups alike. The Hawthorne effect shares some similarity with a type of response bias called demand characteristics, that describes the tendency of research participants to adapt their behaviour or responses to fulfil their purpose in the study, that is, to support what they believe is the aim of the study.<sup>207</sup>

### **Subject-expectancy effects**

Another potential source for bias toward improvement may be subject-expectancy effects, which describe the effects of the research subjects' expectation of an effect on their reported outcome.<sup>208</sup> This type of bias includes placebo and nocebo effects. In the DEP.PAIN.DEM trial, subject-expectancy effects may occur in the proxy raters who have delivered the intervention. Because they may subconsciously expect the intervention to be effective (or to cause harm), they may be biased toward reporting an improvement (or worsening) from baseline.

### **Sampling bias**

By applying multiple inclusion and exclusion criteria, the percentage of the target population that is eligible for inclusion is reduced. Furthermore, the likelihood of being included in the trial may differ across the target population, thus introducing risk of sampling bias which may limit the external validity or generalisability of the

---

results.<sup>209,210</sup> In the DEP.PAIN.DEM trial, strict inclusion and exclusion criteria were necessary in order to reduce the risk of harm to frail and multimorbid individuals. This means that the results should not be generalised beyond the population that was in fact eligible to be included in the trial. Although we were able to include a small percentage of all nursing home patients, the obtained results may provide valuable information for clinicians who regularly encounter people with advanced dementia and depression in whom pain is difficult to diagnose, but cannot be ruled out as a potential cause for distressing symptoms.

### **5.2.5 Controlling for bias**

Although proxy-rated data have a high risk of bias, the placebo-controlled design of the DEP.PAIN.DEM trial ensures that caregiver characteristics which may influence our results are balanced between the active and placebo groups, thus minimising the effects of any bias introduced from proxy rating. This is one of the most important advantages of the DEP.PAIN.DEM trial in comparison with the previous cluster-randomised controlled trial by Husebo et al. which generated the main hypothesis that the DEP.PAIN.DEM trial was designed to test.<sup>39</sup> However, due to risk of sampling bias, the results should not be generalised beyond the target population: nursing home patients with moderate-to-severe cognitive impairment and depressive symptoms who do not have diagnosable severe pain, do not use regularly scheduled opioid analgesics other than or exceeding buprenorphine 5 µg/hour, and do not fulfil other exclusion criteria as listed in section 3.4.2.

## 5.3 Discussion of the results

Paper I confirmed that pain is associated with increased depressive symptoms in people with advanced dementia. This result corresponds to similar findings from cross-sectional studies, but our study was the first to show that change in pain intensity between baseline and follow-up was associated with a corresponding change in depressive symptom burden at individual level.<sup>152,211</sup>

In Paper II, we found that despite the relationship between pain and worsening of depression, analgesic treatment was not associated with reduced depression scores in people with advanced dementia and depression. In contrast, active treatment was associated with more persistent depressive symptoms compared to those who received placebo. This was mainly driven by a significant decrease in depressive symptoms from baseline to follow-up in the placebo group, while depressive symptoms in the active treatment group remained unchanged. We suggest that this unexpected finding is at least partly explained by adverse effects of analgesic treatment. This is supported by the high dropout rate observed in participants treated with buprenorphine TDS compared to placebo TDS, which was not observed in those who received paracetamol.

Paper III investigated the tolerability and adverse events reported in the subgroup of participants who received buprenorphine or placebo TDS, and found a significantly higher hazard ratio for discontinuation due to adverse events in those who received buprenorphine compared to placebo. Furthermore, antidepressant use was strongly associated with increased risk for discontinuation of active treatment, suggesting a clinically significant drug interaction between buprenorphine TDS and antidepressants in people with advanced dementia. Other variables investigated, including cognitive function, pain intensity, depressive symptoms, and use of other psychotropic or anticholinergic drugs, did not impact discontinuation risk. The most frequent types of adverse events associated with discontinuation were psychiatric and neurological, and sedation was the single most frequently reported adverse symptom.

---

### 5.3.1 The course of depressive symptoms in dementia

A large study by Borza et al. including 1158 nursing home residents at baseline ( $T_0$ ) with follow-up after 12 ( $T_1$ ), 31 ( $T_2$ ), 53 ( $T_3$ ), and 74 months ( $T_4$ ) found that the mean CSDD score decreased from  $T_0$  to  $T_1$ , but returned to baseline level at  $T_2$ .<sup>53</sup> The authors suggest that this rebound effect may be caused by a Hawthorne effect, which has also been observed in other studies of depressive symptoms in dementia.<sup>39,53</sup> In Paper I, we observed a similar decrease of CSDD depressive symptoms in the REDIC population who had follow-up after 6 months, but not in the COSMOS population who were re-assessed after 4 months. This may be due to lower sample size and shorter time to follow-up in the latter group.

In Paper II, we found a significant decrease of depressive symptoms in the placebo group after a 13-week follow-up period. While this group was smaller and had even shorter time to follow-up compared with the COSMOS group, participants in the DEP.PAIN.DEM trial were selected to include people with high initial levels of depression, thus making it more likely to observe a change in depressive symptoms over time. The apparent decrease of depressive symptoms in the DEP.PAIN.DEM control group may therefore be caused by regression toward the mean, which describes an effect where extreme measurements tend to normalize upon repeated assessments, as well as by a Hawthorne effect similar to that described in previous prospective studies.

### 5.3.2 The efficacy of analgesic treatment for depression in people with dementia

In the DEP.PAIN.DEM trial, those who received active analgesic treatment had an unchanged mean CSDD score from baseline to follow-up, and the treatment effect was therefore in the direction of increased depressive symptoms relative to the observed improvement in the placebo group. This result directly opposes our initial hypothesis which was based on results from a previous trial,<sup>39</sup> and other findings suggesting that pain may contribute to depression in dementia.<sup>145-149,152</sup>

Husebo et al. conducted the only previous study assessing the effect of analgesic treatment on depressive symptoms in people with advanced dementia, and found a moderate improvement on depression assessed by the NPI-NH depression item and a large improvement in the NPI-NH mood syndrome consisting of the items depression, apathy, anxiety, night-time behaviours and appetite and eating disorders.<sup>39</sup> However, the NPI-NH depression item did not show improvement in the DEP.PAIN.DEM trial. Effects on the NPI mood cluster and other NPI items have not yet been investigated in the DEP.PAIN.DEM data; this should be a future priority.

Other methodological differences between the DEP.PAIN.DEM trial and the previous trial by Husebo et al. may have contributed to the different results. The latter included nursing home patients with advanced dementia and agitation, and like the DEP.PAIN.DEM trial, participants were included regardless of presumed pain intensity at baseline.<sup>39</sup> However, in the trial by Husebo et al., pain intensity assessed by MOBID-2 at baseline was higher compared with the DEP.PAIN.DEM trial (mean total score approximately 4 and 3, respectively).<sup>155</sup> Higher pain intensity may have contributed to a greater potential for beneficial treatment effects in the trial by Husebo et al. in comparison with our study. Husebo et al. found that over 60% had moderate-to-severe pain, defined as a MOBID-2 score of 3 or more at baseline, and that pain treatment significantly reduced pain intensity.<sup>38,155</sup>

The trial by Husebo et al. also had a larger sample size, with 352 participants in total of whom 175 were cluster randomised to receive the intervention, and 177 to the control condition which was usual treatment.<sup>38</sup> In the intervention group, 63% (n=103) were prescribed paracetamol and only 22.6% (n=37) received buprenorphine, as opposed to 45.0% (n=36) and 55.0% (n=44) of the DEP.PAIN.DEM intervention group. This means that a higher proportion of participants in the former trial used either no analgesic or low-dose paracetamol at inclusion, and were allocated to receive paracetamol only. The different allocation ratio to paracetamol and buprenorphine between the two trials is a possible explanation for the apparently opposing results. The stepwise protocol for treating pain that was applied by Husebo et al. included the option to use pregabalin for

---

neuropathic pain, and found that this was the major cause of dropouts due to adverse events, with two dropouts (17%) among the 12 participants who were prescribed pregabalin. Those who received pregabalin also used paracetamol and buprenorphine TDS.

Because the DEP.PAIN.DEM trial was placebo-controlled, and both treatment groups were well balanced with regard to demographic and clinical characteristics, the increased stability of depressive symptoms in the active treatment group compared to the controls is unlikely to be explained by measuring error, proxy bias or expectation effects. Therefore the administered analgesic treatment (paracetamol and/or buprenorphine) must have had some impact on the symptoms that were assessed and interpreted as depression using the CSDD scale.

Subgroup analyses of the effects of paracetamol and buprenorphine did not show a significant effect on change in total CSDD score in any of the treatment groups, possibly due to low sample size. There was a trend toward increased depressive symptoms from baseline to 13 weeks in both groups, with a treatment effect of 1.98 ( $p=0.162$ ) and 3.04 ( $p=0.059$ ) for paracetamol and buprenorphine, respectively. There are many potential factors which may influence the course of depressive symptoms in people with advanced dementia, and analgesics may be effective in subgroups of patients. Further studies of the association between pain and depression are therefore needed, and larger sample sizes with increased statistical power are likely required.

### **5.3.3 The DEP.PAIN.DEM trial: Adverse events and safety**

In multimorbid nursing home patients with advanced dementia, a high rate of clinical deterioration and death can be expected over a 12-week period.<sup>212</sup> Of the thirteen participants who were reported to deteriorate and/or died during the trial, none were suspected to be related to the study treatment or procedures. In all thirteen reported cases, the study treatment was discontinued upon recognition of worsened health and none of the participants who died still received treatment with the study drug at the time of death. Furthermore, the number of deteriorations and deaths did not differ significantly between active treatment and placebo.

Although we had a high number of withdrawals from treatment with buprenorphine because of adverse events, these were typically mild and all resolved upon discontinuation of treatment. The number of drug discontinuations shows that the procedures to ensure patient safety were successfully implemented in the nursing homes, and illustrates the carers' and the responsible physicians' awareness of and commitment to patient safety.

### **5.3.4 Differentiation between symptoms of dementia, depression, and adverse events**

As mentioned previously, the CSDD items can be clustered into five factors, comprising one mood factor and four non-mood factors.<sup>178</sup> Of these, mood and cyclic functions appear to remain stable while other non-mood factors increase in severity when dementia progresses and may therefore reflect dementia symptoms rather than true depression.<sup>178</sup> We have not yet investigated the effects of analgesic treatment on the CSDD five factor structure, and cannot conclude as to whether the significant difference between participants who received active treatment and the control group in the course of CSDD symptoms during the follow-up period can be explained by adverse effects of active treatment on mood or non-mood CSDD factors. This will be investigated further by our group.

We suggest that adverse effects of analgesic treatment may have caused worsening of single CSDD items such as reduced appetite, agitation, or sedation, which has cancelled out the Hawthorne effect that was observed in the placebo group. This is supported by preliminary analyses, which do not show any significant worsening of the CSDD mood factor during treatment, while several non-mood factors worsened significantly (manuscript in preparation). The estimated effect of active treatment (paracetamol/buprenorphine) on the CSDD mood factor from baseline to 13 weeks was 0.76 ( $p=0.08$ ), while the effect on the combined non-mood factors was 1.65 ( $p=0.03$ ). The non-mood factors behaviour and retardation worsened significantly by 0.72 ( $p=0.01$ ) and 1.14 ( $p=0.01$ ), respectively, while the factors physical and cyclic symptoms remained unchanged ( $p=0.88$  and 0.71, respectively). Subgroup analyses show that the buprenorphine group, but not the paracetamol group, had a significant

---

worsening of non-mood CSDD factors during treatment. In those who received buprenorphine, the treatment caused significant worsening of the factors behaviour and retardation by 0.97 ( $p=0.01$ ) and 1.53 ( $p=0.01$ ), respectively, from baseline to 13 weeks. No significant treatment effect on any factor was found in the paracetamol group. This supports the hypothesis that adverse effects of buprenorphine on dementia symptoms may explain the lack of improvement on depressive symptom in the DEP.PAIN.DEM intervention group.

### **5.3.5 Adverse effects of buprenorphine in people with dementia**

With the exception of Husebo et al., no previous trial has reported on the safety of buprenorphine TDS in people with advanced dementia.<sup>38,155</sup> Husebo et al. found that buprenorphine was well tolerated, and of the 40 participants who received an opioid analgesic in the previous trial (36 of whom received buprenorphine TDS), only four were withdrawn because of adverse events which the researchers deemed likely to be treatment related. The prevalence and types of adverse events recorded in those who received buprenorphine were not reported.<sup>38,39,155,213</sup>

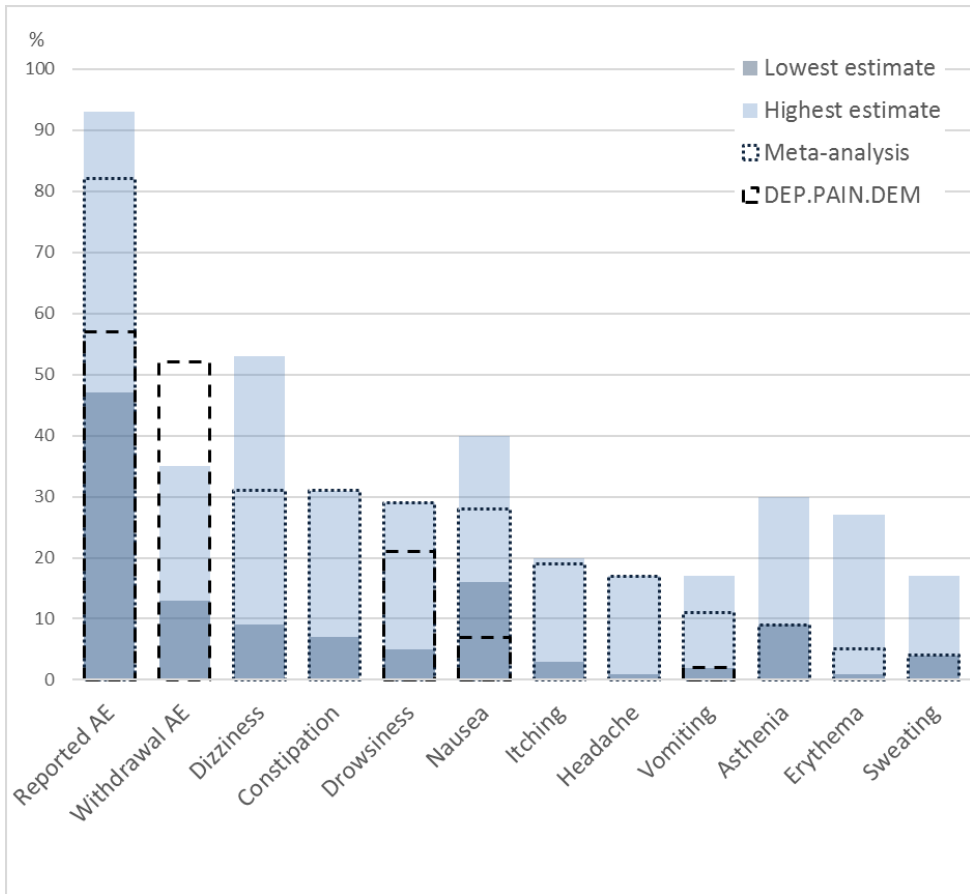
The pattern of observed adverse events from buprenorphine treatment as described in Paper III differs from previous results from studies that have included elderly people without dementia in several important ways. A non-systematic literature search identified five trials and one meta-analysis that have reported on the safety of buprenorphine for chronic moderate-to-severe pain in cognitively intact elderly people, excluding those which exclusively recruited patients with postoperative or cancer-related pain.<sup>214-219</sup> All five trials had an open-label design. While the minimal age of the included participants ranged from 58 years, the mean age was high with a range from 72 to 85 years, and the combined number of participants in all five trials was 841. The follow-up period ranged from four to 22 weeks, with a median duration of 12 weeks. The meta-analysis included some additional trials which did not originally report adverse events stratified on age group. However, eight of the 14 controlled trials included in the meta-analysis had an enriched enrolment design, meaning that only participants who tolerated treatment for an open-label run-in



period were enrolled in the randomised controlled trial.<sup>219</sup> Figure 5 displays the observed range of the most frequently self-reported adverse events in the five controlled trials, and corresponding results from the meta-analysis of six non-enriched trials and Paper III.

Two trials found lower rates of reported adverse events compared with the DEP.PAIN.DEM trial (both previous trials found a rate of 47%, compared with 57% in the DEP.PAIN.DEM trial),<sup>215,218</sup> while the three other trials and meta-analysis reported adverse events in 82-93% of the participants.<sup>214,216,217,219</sup> However, most adverse events were classified as mild-to-moderate, and did not cause withdrawal from treatment (Figure 5). Subjectively rated adverse events such as dizziness, nausea, constipation, asthenia, and headache were either not reported or had a much lower occurrence in the DEP.PAIN.DEM trial compared with trials that included elderly people without dementia (Figure 5).

Methodological differences may have influenced the observed differences in adverse events between the DEP.PAIN.DEM trial and the previous studies that have included elderly people without dementia (Figure 5). The administered doses ranged from 5-70 µg/hour in the previous trials, and most included a larger number of participants compared to our study.<sup>214-219</sup> This increases the likelihood of reports of dose-dependent or rare adverse events. Furthermore, because the trials did not have a double-blinded placebo-controlled design and not all had a control group, there is inherent risk of different types of bias such as expectancy or confirmation bias which may lead to over-reporting of adverse events and cannot be controlled for in the data material. Other participant characteristics such as pain diagnosis and pain intensity may also have had an impact on the prevalence and pattern of adverse effects, particularly because diagnosable pain was not an inclusion criterion for the DEP.PAIN.DEM trial as opposed to the comparator trials.



**Figure 5. Pattern of observed adverse events during treatment with buprenorphine TDS for chronic non-malignant pain in cognitively intact elderly people,<sup>214-219</sup> compared with results from the DEP.PAIN.DEM trial (Paper III).** AE; adverse event, DEP.PAIN.DEM; Efficacy of pain treatment on depression in people with dementia, TDS; transdermal system

However, the most important difference between our trial and the previous trials conducted in elderly people without dementia is arguably our reliance on proxy rating. It is unlikely that people with dementia are less affected by adverse events than those without dementia. Rather, the proxy raters may not have had the proper tools, education, and resources to observe all types of adverse events, symptoms may be expressed differently in people with dementia, and/or the observable symptoms may have been too subtle to detect by proxy. As an example, it seems possible that

dizziness could be interpreted as other symptoms such as confusion or sedation in people who cannot communicate verbally. In any case, insufficient ability to detect or correctly identify mild-to-moderate adverse events is a likely explanation for the discrepancy illustrated in Figure 5.

Although certain adverse effects may have been interpreted differently or attributed to other symptoms by the proxy raters, the high number of treatment discontinuations illustrates their commitment to patient safety. This may also have contributed to the high rate of treatment discontinuations. Many adverse events of buprenorphine TDS are considered transient and may resolve upon continued treatment, but the decision to wait and see may be easier to make in patients who do not have communication difficulty.

Interestingly, the patterns of adverse events reported in people with dementia during different pharmacological interventions have recently been investigated in a systematic review, which found similar results to those reported in Paper III: neurological and psychiatric adverse events were among the most frequently reported adverse events across different studies; centrally active drugs were among those most often implicated in adverse events; and the frequency of reported adverse events was generally lower in people with dementia compared to those without dementia.<sup>220</sup> Nevertheless, this does not imply that people with dementia are less exposed to adverse effects, as other trials have identified dementia as a risk factor for adverse drug reactions.<sup>221</sup>

While we were able to detect fewer than expected adverse events of buprenorphine TDS in people with dementia in the DEP.PAIN.DEM trial, particularly those of mild-to-moderate intensity, we found a higher than expected rate of withdrawal due to adverse events (Figure 5) and a higher relative frequency of psychiatric and neurological adverse events. In 16 of 17 cases, these were deemed mild-to-moderate in severity by the responsible physicians, in the sense that continued treatment would be inappropriate - only one participant had mild/transient sedation and continued treatment.

---

The DEP.PAIN.DEM trial appears to be poorly designed to detect common mild-to-moderate adverse effects of buprenorphine TDS, such as dizziness, which do not necessarily cause any easily observable symptoms. However, the adverse events that were recorded differ significantly from the pattern of adverse effects previously reported in elderly people without dementia. Most importantly, a higher than anticipated proportion of the participants discontinued treatment because of adverse events, and psychiatric and neurological adverse events were reported more frequently in people with advanced dementia compared with previous trials in cognitively intact elderly people.

### **5.3.6 Sedation and reduced daytime activity during buprenorphine use**

Mild and transient drowsiness or sedation is a common adverse effect of buprenorphine TDS, estimated to affect approximately 29% in studies that have included people aged 65 or more without dementia.<sup>219</sup> Change in daytime activity was a secondary outcome in Paper III, with daytime activity arbitrarily defined as the total activity output recorded by actigraphy between 09:00 AM and 09:00 PM. We found that those who received buprenorphine had significantly reduced daytime activity shortly after treatment was started compared with the placebo group which had unchanged activity. However, we do not know whether reduced daytime activity is transient and may resolve upon continued treatment with buprenorphine in people with dementia. Should a reduction in activity level persist during long-term treatment, this may contribute to increased risk for functional decline, frailty, and mortality.<sup>222-</sup>  
<sup>225</sup> In light of the potential serious consequences of a lasting decrease in daytime activity, the long-term effects of buprenorphine TDS on activity and function in people with dementia should be investigated further.

### **5.3.7 Interaction between buprenorphine TDS and antidepressants**

In Paper II, we found that antidepressant drug use was the only variable for concomitant drug use which had an impact on the tolerability of buprenorphine TDS. Even though relatively few individuals who received buprenorphine used

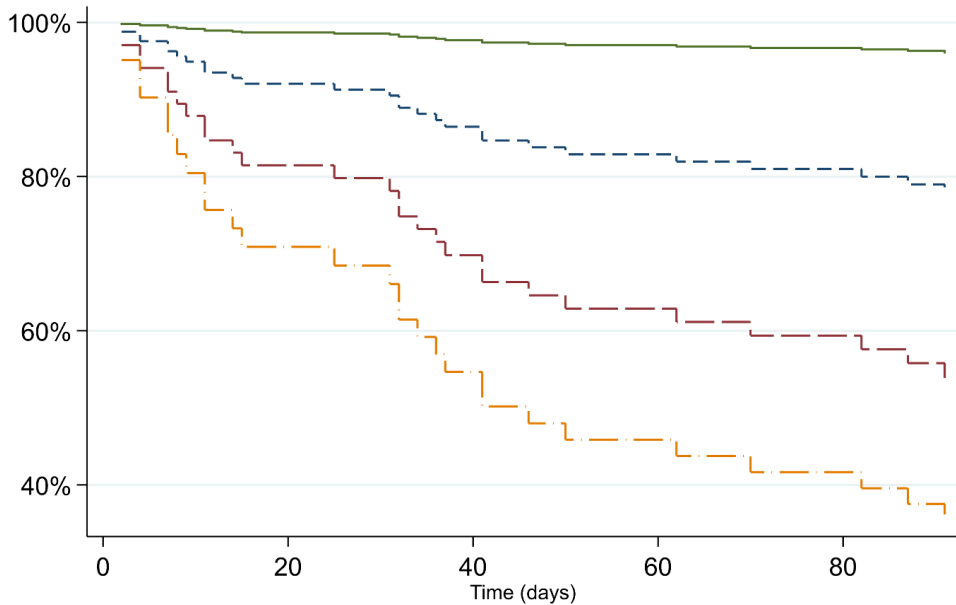
antidepressants (n=14), we found that those who did were at the highest risk of discontinuation of treatment due to adverse events. When analyses were stratified on antidepressant use, those who did not use antidepressants did not have significantly increased risk of discontinuation during buprenorphine treatment compared with placebo, as illustrated in Figure 6. Even though the number of participants who received active treatment and did not use antidepressants was higher (n=30), we did not find a statistically significant increase in discontinuation risk in this group compared with antidepressant nonusers who received placebo (n=18; Figure 6). In comparison, the 14 individuals who used antidepressants and received buprenorphine had a large, statistically significant risk increase compared with those who used antidepressants and received placebo (n=27; Figure 6).

Although subgroup analyses must be interpreted with caution due to low sample size, this highly significant effect suggests that a drug interaction between antidepressants and buprenorphine, rather than adverse effects of buprenorphine alone, may be the mechanism behind the low tolerability of buprenorphine TDS observed in the DEP.PAIN.DEM trial. An interaction between buprenorphine and antidepressant drugs has not previously been specifically described in the literature.

Of those who received buprenorphine and used antidepressants, seven used escitalopram, five used mirtazapine, and two used mianserin. Within each antidepressant group, four, three, and two participants, respectively, had adverse events which led to premature discontinuation of treatment.

Combinations of drugs with either serotonergic or anticholinergic activity are known to cause clinically relevant interactions in frail elderly people. Antidepressants of the SSRI class may cause serotonin toxicity, particularly in combination with other drugs that cause increased central serotonin levels.<sup>226</sup>

Escitalopram is an SSRI with strong serotonergic properties, and the most frequent adverse effects include diarrhoea, dizziness, xerostomia, fatigue, headache, nausea, sweating, sedation, and tremor.<sup>227,228</sup>



<b>Discontinuation risk in antidepressant users:</b>	
— Placebo	- - - Buprenorphine
Hazard ratio 26.1, 95% CI 3.35; 203, p=0.002	
<b>Discontinuation risk in antidepressant nonusers:</b>	
- - - Placebo	— Buprenorphine
Hazard ratio 2.47, 95% CI 0.77; 7.97, p=0.130	

**Figure 6. Discontinuation risk stratified by antidepressant use**

Cox regression, adjusted for age and sex. CI, confidence interval.

Mirtazapine and mianserin are tetracyclic antidepressants (TeCAs) which act as NaSSAs. Mirtazapine acts as an antagonist on the  $\alpha_2$ -receptors of the adrenergic system, as well as on several 5-HT receptor subtypes, thereby enhancing serotonergic activity.<sup>229</sup> Dry mouth, sedation, and increases in appetite and body weight are the most common adverse effects.<sup>229</sup> Mianserin has a similar pattern of activity.<sup>230</sup>

A potential mechanism for the observed interaction may be additive or synergistic effects of buprenorphine and antidepressants on sedation, as all the types of

antidepressants used may cause sedation. This is also supported by reports of increased sedation as the most frequent adverse effect of buprenorphine in the DEP.PAIN.DEM trial. However, we did not find that sedation or somnolence was reported more frequently in those who received buprenorphine and used antidepressants compared with those who did not (Pearson  $\chi^2$ -test,  $p=0.913$ ).

Another potential explanation for the observed interaction may be the antagonistic effects of buprenorphine on the opioid  $\kappa$ -receptor. Activation of the  $\kappa$ -receptor causes adverse effects such as hallucination, dysphoria, increased anxiety, and aversion, in addition to analgesic effects.<sup>114,157,158</sup> In contrast to full opioid agonists such as morphine and oxycodone which activate the  $\kappa$ -receptor, buprenorphine acts as a  $\kappa$ -receptor antagonist and is therefore associated with a lower risk of treatment-induced dysphoria. Antidepressants exert their effects on the monoamine neurotransmitter systems, and an emerging body of evidence suggests that  $\kappa$ -receptors also modulate dopaminergic and serotonergic signalling.<sup>231</sup> Although the precise mechanism of action is not yet understood, the  $\kappa$ -receptor modulates the regulation of serotonin, including the activity of the presynaptic serotonin transporter (SERT).<sup>163</sup> SERT regulates the synaptic availability of serotonin (5-HT) by transporting released 5-HT back from the synaptic cleft into the neuron, and is the primary site of action for SSRIs.<sup>228</sup> Preclinical trials have shown that activation of the  $\kappa$ -receptor may decrease SERT expression and activity, thereby decreasing 5-HT reuptake, in some regions where the  $\kappa$ -receptor is expressed.<sup>231,232</sup>  $\kappa$ -receptor agonists also increase dopamine transporter activity, but have no effect on noradrenergic transporter activity.<sup>233</sup>

However, most research on the  $\kappa$ -receptor system has been conducted in rodent models. Little evidence exists in support of increased serotonergic activity during treatment with buprenorphine, and the effects of buprenorphine on the monoamine system have not been investigated in people with dementia.<sup>234-236</sup>

Even though buprenorphine has some anticholinergic effects, such as xerostomia and urinary retention, it is unlikely that combined anticholinergic effects have caused the observed interaction for two reasons: firstly, ACB score did not impact

---

discontinuation risk, and secondly, none of the participants who received buprenorphine used TCAs.

Frailty may also contribute to the increased risk of adverse events in those who used antidepressants and received buprenorphine, as frail individuals are characterised by impaired homeostasis and reduced resilience which increases their susceptibility to adverse drug effects and drug interactions.<sup>237</sup> However, this does not explain why antidepressants were the only drug class to impact discontinuation risk.

As shown in Figure 6, the major difference in tolerability of buprenorphine TDS was not found between those who received buprenorphine versus placebo, but rather between those who used antidepressants and buprenorphine in combination versus those who did not. This suggests that buprenorphine TDS should be used with particular caution in people with dementia who also use antidepressants. New clinical trials with larger sample sizes are needed to fully elucidate the impact of concomitant drug use on risk of adverse events of buprenorphine TDS, and also to determine whether antidepressant use increases the risk of adverse events during treatment with other strong opioids in addition to buprenorphine TDS.

### **5.3.8 Challenges concerning research in people with dementia**

Nursing home patients with dementia are among the most difficult groups to include in research. Those who are granted long-term residential care in Norway have advanced dementia and/or complex comorbidity with severely reduced independence and functional ability. While most are being treated for multiple comorbid conditions, the individual pharmacological interventions often lack evidence-based efficacy and safety when applied in combination to patients with advanced disease and frailty. Most randomised controlled trials that compare an intervention with either placebo or the best available treatment are conducted in relatively healthy patients who do not have clinically significant comorbid conditions, and who are capable of providing consent to participate as well as to self-report symptoms and adverse effects during treatment.<sup>238</sup>



The DEP.PAIN.DEM trial required screening of a high number of individuals from many nursing homes in order to achieve the desired number of included participants. Of those who fulfilled all of the inclusion criteria and none of the exclusion criteria, 51% gave informed consent and were enrolled in the trial. The corresponding inclusion rate for a previous large-scale placebo-controlled trial by Banerjee et al. which assessed the efficacy of antidepressant treatment versus placebo for depression in people with dementia was 53.5%.<sup>74</sup> However, the latter trial included participants from old-age psychiatry services where only 664 patients were screened for eligibility in order to obtain enrolment of the required 326 participants.<sup>74</sup> This shows that the identification of eligible participants with dementia and depression was more resource-intensive in the nursing home setting compared to specialized secondary health care services.

## **5.4 External validity**

Paper I included a large sample of nursing home patients with dementia of varying severity. Data were obtained from two different studies, conducted in a high number of nursing homes of varying sized, from a large and varied geographical area. In Paper I, we found a strong association between pain intensity and depressive symptoms in people with dementia, which we believe has high clinical relevance for this population. Based on these findings, pain should be recognized as a risk factor for depression, and vice versa, in nursing home patients and people with dementia.

We recruited participants from nursing homes of varying sizes, located in both urban and rural areas, and recruited from a large geographical area. Although a high number of nursing home patients were screened to identify eligible participants for the DEP.PAIN.DEM trial, this does not mean that the trial had a poor inclusion rate. Most of the screened nursing home patients were excluded based on information from medical records, such as use of opioid analgesics, short-term placement, no dementia, other diagnoses, et cetera. An acceptable ratio of those who were eligible to participate were included in the trial. Therefore, the participants are representable for the population that was studied: nursing home patients in Norway with dementia and

---

depressive symptoms, who neither had diagnosable severe pain which precluded randomisation to active or placebo conditions, nor used other opioid analgesics. We expect that the obtained results from the DEP.PAIN.DEM trial and Papers II and III have direct clinical applicability for this group.

However, patterns of analgesic use in people with dementia vary greatly between different countries. Both the general prevalence of analgesic use, as well as the choice of analgesic agent and doses applied may vary between different countries and clinical settings. We excluded 28% of all nursing home patients who were screened because they already received non-permitted treatment with an opioid. Therefore, the findings may not be applicable to clinical settings where fewer receive analgesic treatment, and more individuals are likely to have undiagnosed and untreated pain.

Additionally, the DEP.PAIN.DEM trial was not designed to investigate whether there was any interaction between the obtained treatment effect and type of pain.

Therefore, the results should not be generalised to populations with specific subtypes of pain, such as neuropathic pain or cancer pain, as well as those with severe pain.

## 5.5 Ethical considerations

The DEP.PAIN.DEM trial and this thesis have been planned and conducted in accordance with the current Declaration of Helsinki.<sup>239</sup> All data material that has been used in this thesis originates from trials that have been approved by the Regional Committees for Medical and Health Research Ethics. In addition, the DEP.PAIN.DEM trial was approved and monitored by the Norwegian Medicines Agency. The DEP.PAIN.DEM, COSMOS, and REDIC trials were all registered in a clinical trial database ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) prior to enrolment of participants, and the data from the trials have been used to test hypotheses stated *a priori*. These results have been disseminated.

The Declaration of Helsinki states that the rights and interests of individual research subjects must be safeguarded in all medical research, that the knowledge that is generated by research should be of direct benefit to the participant, and that it must

outweigh burden and potential harm.<sup>239</sup> For people who are particularly vulnerable, and may have increased likelihood of being wrongfully treated or harmed, the Declaration calls for specifically considered protection.<sup>239</sup> Furthermore, the Declaration provides criteria for consent to participate in research. Whenever possible, research should be conducted in subjects who are able to give free and voluntary informed consent to participation. However, when necessary, people who cannot provide informed consent may be included in research as long as informed consent is obtained from a legally authorised representative. In such cases, the research must either be likely to benefit these participants directly, or to promote the health of the group that they represent. For these reasons, the risk-benefit balance must be considered particularly carefully when research involves people with advanced dementia, many of whom are unable to provide informed consent and have difficulty communicating their wishes and needs.

Regardless of whether the participant had capacity to consent, their ability to provide active assent or dissent during trial procedures was respected and no participant was forced to take study treatment or complete any assessment against their will. All those who were approached received individually adjusted verbal and written information about the trial, to ensure as far as possible that they were aware of the aims and implications of participating in the trial regardless of whether the participants themselves or their next of kin/legal guardian provided informed consent.

Some important procedures that were implemented in the protocol in order to reduce the risk of harm will be discussed here. Firstly, in order to reduce the risk of untreated pain in participants who were randomised to receive placebo, the use of as-needed analgesics was allowed and encouraged, and the responsible physician had full authority to withdraw the patient from participation in the trial if they deemed it necessary, for example because of difficulty in managing pain, or clinical changes with increased need for pain management, such as falls, injuries or infections. Although the control condition was a placebo, no ongoing analgesic treatment was removed. Therefore, the placebo condition can be considered current best practice.<sup>239</sup> Secondly, because participants who did not necessarily have diagnosable pain at

---

baseline were prescribed a strong opioid analgesic “off-label” with depressive symptoms as the primary indication, they may be exposed to risk for adverse effects without direct benefit on pain or other symptoms. In order to minimise the risk of harm, the use of buprenorphine TDS was limited to the lowest available dose. No participant was prescribed buprenorphine/placebo TDS without the approval of the responsible physician who had complete knowledge of the patient’s clinical state, usual medical treatment, potential drug interactions, and so forth. Furthermore, the nursing homes received thorough information about potential adverse effects, and were closely followed by the researchers in order to detect and manage adverse events immediately.

Unfortunately, a breach of protocol was discovered after the DEP.PAIN.DEM trial was completed. The Norwegian Medicines Agency approved the use of buprenorphine TDS in the stepwise protocol for treating pain, with the condition that no participants would receive an opioid analgesic as part of the trial unless they already received other scheduled analgesic treatment (e.g. paracetamol). This condition was made in order to reduce the risk of opioid dependency in participants who did not have pain. However, the stepwise protocol for treating pain was applied as described in Table 6 (page 67) which allows for prescribing buprenorphine/placebo TDS to participants who did not use any analgesic, but had difficulty swallowing tablets. We found that eleven participants were affected by this error, seven of whom received buprenorphine, and four received placebo TDS. Anonymized details of these participants including the occurrence of adverse events as a result of the protocol violation have been shared with the Norwegian Medicines Agency and the Regional Committee for Medical and Health Research Ethics. Four of the seven participants who received buprenorphine had clinically significant pain ( $\text{MOBID-2} \geq 3$ ), and therefore the intervention had a clear indication and was medically justified. One patient had missing data for pain measurement. The rate of adverse effects among the seven affected participants was lower than the overall rate observed in the trial, and the reported adverse effects were all mild and transient. Because no participants were harmed, the Norwegian Medicines Agency have

released a statement to conclude that no additional investigation in this matter is deemed necessary based on the current available information.

Despite the risk of opioid adverse events in the study being higher than anticipated, these events were generally mild-to-moderate and resolved upon discontinuation of treatment. There was no significant difference in the rate of clinical deterioration or death between buprenorphine and placebo TDS, and no deaths were considered likely to be related to the treatment.

The rationale for the DEP.PAIN.DEM trial was based on data from previous research which indicated that neuropsychiatric symptoms of dementia, including depression, and pain was ameliorated by analgesic treatment with paracetamol or buprenorphine TDS, with low risk of adverse effects.<sup>38,39,155,213</sup> Therefore we expected that those who received the intervention would benefit directly from a reduction of distressing symptoms. We also expected that the control group would benefit directly from improved care after the staff was trained in the assessment of pain and distressing symptoms.

Although the trial did not find a treatment effect of analgesic treatment on depressive symptoms, the knowledge gained from the DEP.PAIN.DEM trial has direct and indirect benefit for the participants for two reasons. Firstly, the trial refutes results from a previous study which found that opioid analgesics may ameliorate depressive symptoms in people with dementia, thus reducing the risk of overprescribing analgesic treatment to people with advanced dementia and depression. Secondly, the DEP.PAIN.DEM trial found a higher than anticipated risk of neurological and psychiatric adverse events in participants treated with buprenorphine, and may contribute to improve detection of adverse effects of buprenorphine TDS in this population. Therefore, although we failed to achieve the anticipated benefit for the participants who received the intervention in the DEP.PAIN.DEM trial, the results have had direct implications for increased safety and knowledge-based treatment recommendations in nursing home patients with advanced dementia.

---

## Conclusions

This thesis has investigated how pain is related to depressive symptoms in people with dementia, and furthermore the efficacy and safety of analgesic treatment for depression in nursing home patients with advanced dementia and depressive symptoms.

In Paper I, we found that pain was associated with increased depressive symptoms in a cohort of nursing home patients with dementia.

However, experimental data from Paper II demonstrate that an individualised increase in analgesic treatment using paracetamol or buprenorphine TDS did not ameliorate depressive symptoms in nursing home patients with moderate to severe dementia and depression compared to placebo. Contrary to our initial hypothesis, we found that active treatment was associated with more persistent depressive symptoms, possibly due to adverse effects of buprenorphine TDS.

Paper III follows up on these results and investigates more closely the observed pattern of adverse events in participants who were prescribed buprenorphine TDS, and reports higher than anticipated rates of adverse events resulting in poor tolerability and high risk of discontinuation. Main reasons for discontinuation were psychiatric and neurological adverse events, which may easily be attributed to neuropsychiatric symptoms in dementia. Secondary analyses also show reduced daytime activity during the first days of treatment. Concomitant use of antidepressants and buprenorphine greatly increased the risk of adverse events, suggesting that drug interaction effects may have contributed to the poor tolerability.

These results may not be generalizable to patients with severe pain, or to countries or populations where people with dementia generally receive less analgesics compared to Norway. The safety and efficacy of buprenorphine TDS for pain in people with dementia should therefore be investigated further, specifically in relation to exacerbation of neuropsychiatric symptoms as well as potentially reduced daytime activity during long-term treatment which may adversely affect clinical outcomes.

## Implications and future perspectives

Currently, the use of both opioid analgesics and antidepressants is at an all-time high in nursing home patients and people with dementia. This change in prescribing practice has not been followed by increased efforts to investigate the safe and effective use of analgesic drugs in frail, multimorbid patients with dementia and high rates of polypharmacy and drug-related problems. One reason for the lack of evidence may be the challenge of designing high-quality randomised controlled trials that are ethically acceptable and feasible in this population. There is also a lack of robust evidence for the efficacy of antidepressants in the treatment of depression in people with dementia, while studies have shown high risk of adverse effects. This indicates the need for better treatment guidelines for both pain and depression in people with dementia.

The DEP.PAIN.DEM trial has provided data for several supplementary analyses which should be conducted in order to follow up on the findings presented here. This includes planned investigations of: long-term effects of increased sedation during treatment with opioid analgesics; effects of buprenorphine TDS on different behavioural and psychiatric symptoms of dementia such as the CSDD factor structure (including mood versus non-mood factors), NPI-NH items and clusters, and CMAI; and effects of paracetamol on daytime activity (actigraphy).

To date, very few placebo-controlled trials of opioid analgesics have been conducted in people with dementia. This thesis has presented important new information about the tolerability and adverse events of buprenorphine TDS in people with advanced dementia and depression. However, the safety data are based on secondary analyses and include a relatively low number of participants. Participants were recruited based on symptoms of depression rather than pain intensity, and we were not able to assess how pain intensity or type of pain affected tolerability. Insufficient evidence exists to determine which opioid analgesics may be superior in terms of tolerability and efficacy in people with dementia. Therefore, more research on the efficacy and safety of buprenorphine and other opioid analgesics for treating pain in people with

---

advanced dementia is needed. Future research should aim to produce clinically relevant information including adverse events, dose recommendations, and drug interactions in this population.

One potential future direction is to conduct a discontinuation trial of opioid analgesics in people with advanced dementia and mild/no pain. If adverse effects of opioid analgesics can be mistaken for neuropsychiatric symptoms in dementia, and cause increased sedation and reduced daytime activity, such symptoms may improve if opioid treatment is discontinued when it is no longer indicated, or unnecessarily high doses are reduced. Furthermore, if concomitant use of antidepressants causes reduced tolerability of buprenorphine TDS, those who also use antidepressants should benefit more from dose reduction or discontinuation of buprenorphine. This hypothesis should be tested for buprenorphine specifically, and opioids in general. As both antidepressants and opioid analgesics are among the most frequently prescribed drugs in nursing home patients with dementia, a drug interaction has high clinical relevance and wide implications for patient safety.

Future trials should be designed to overcome the challenges that are inherent to research on people with dementia in the nursing home setting; including how to achieve an appropriate control condition. Placebo-controlled trials are particularly difficult in multimorbid participants with complex treatment needs, and current best practice may be preferable to a placebo comparator in many cases. However, for many types of interventions, including non-pharmacological or multicomponent interventions, blinding is difficult to obtain. Lack of blinding may increase the risk of bias, thus reducing the quality of the obtained results.

There is still a need for high-quality research to inform the safe and effective treatment of pain and depressive symptoms, using both pharmacological and non-pharmacological strategies, to improve clinical outcomes and quality of life for people at all stages of dementia.



---

## References

1. Prince M, Wimo A, Ali G, et al. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. *London: Alzheimer's Disease International* 2015.
2. Prince M, Ali G-C, Guerchet M, et al. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res Ther* 2016;8:23.
3. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017;390:2673-734.
4. Wimo A, Guerchet M, Ali G-C, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement* 2017;13:1-7.
5. Laver K, Dyer S, Whitehead C, et al. Interventions to delay functional decline in people with dementia: a systematic review of systematic reviews. *BMJ Open* 2016;6:e010767.
6. Luppá M, Luck T, Weyerer S, et al. Prediction of institutionalization in the elderly. A systematic review. *Age Ageing* 2010;39:31-8.
7. Luppá M, Luck T, Brahler E, et al. Prediction of institutionalisation in dementia. A systematic review. *Dement Geriatr Cogn Disord* 2008;26:65-78.
8. Cepoiu-Martin M, Tam-Tham H, Patten S, et al. Predictors of long-term care placement in persons with dementia: a systematic review and meta-analysis. *Int J Geriatr Psychiatry* 2016;31:1151-71.
9. Risco E, Cabrera E, Jolley D, et al. The association between physical dependency and the presence of neuropsychiatric symptoms, with the admission of people with dementia to a long-term care institution: A prospective observational cohort study. *Int J Nurs Stud* 2015;52:980-7.
10. Brodaty H, Connors MH, Xu J, et al. Predictors of institutionalization in dementia: a three year longitudinal study. *J Alzheimers Dis* 2014;40:221-6.
11. Statistics Norway (Statistisk sentralbyrå). Care services, 2015. <https://www.ssb.no/helse/statistikker/pleie/aar/2016-06-29>. Published 29.06.2016; accessed 02.11.2017.
12. Helvik AS, Engedal K, Benth JS, Selbaek G. Prevalence and severity of dementia in nursing home residents. *Dement Geriatr Cogn Disord* 2015;40:166-77.
13. Røen I, Selbæk G, Kirkevoold Ø, et al. Resource Use and Disease Course in dementia - Nursing Home (REDIC-NH), a longitudinal cohort study; design and patient characteristics at admission to Norwegian nursing homes. *BMC Health Serv Res* 2017;17:365.
14. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular types. *Biomed Res Int* 2014;2014:908915.
15. Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. *Lancet* 2011;377:1019-31.
16. Pini L, Pievani M, Bocchetta M, et al. Brain atrophy in Alzheimer's Disease and aging. *Ageing Res Rev* 2016;30:25-48.
17. Shaw CM, Alford EC, Jr. Neuropathology of the limbic system. *Neuroimaging Clin N Am* 1997;7:101-42.
18. Lui JH, Hansen DV, Kriegstein AR. Development and evolution of the human neocortex. *Cell* 2011;146:18-36.
19. Frith C, Dolan R. The role of the prefrontal cortex in higher cognitive functions. *Brain Res Cogn Brain Res* 1996;5:175-81.

20. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol* 2012;71:362-81.
21. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med* 2014;44:673-83.
22. Aarsland D, Rongve A, Nore SP, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. *Dement Geriatr Cogn Disord* 2008;26:445-52.
23. Koedam EL, Pijnenburg YA, Deeg DJ, et al. Early-onset dementia is associated with higher mortality. *Dement Geriatr Cogn Disord* 2008;26:147-52.
24. Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol* 2008;7:812-26.
25. Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. *Lancet Neurol* 2005;4:752-9.
26. Khan A, Kalaria RN, Corbett A, Ballard C. Update on vascular dementia. *J Geriatr Psychiatry Neurol* 2016;29:281-301.
27. Carotenuto A, Rea R, Colucci L, et al. Late and early onset dementia: what is the role of vascular factors? A retrospective study. *J Neurol Sci* 2012;322:170-5.
28. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 2007;6:442-55.
29. Finkel SI, Costa e Silva J, Cohen G, et al. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr* 1996;8 Suppl 3:497-500.
30. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44:2308-14.
31. Selbaek G, Kirkevold O, Sommer OH, Engedal K. The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, nursing home version (NPI-NH). *Int Psychogeriatr* 2008;20:375-82.
32. Bergh S, Engedal K, Roen I, Selbaek G. The course of neuropsychiatric symptoms in patients with dementia in Norwegian nursing homes. *Int Psychogeriatr* 2011;23:1231-9.
33. Lyketsos CG, Breitner JC, Rabins PV. An evidence-based proposal for the classification of neuropsychiatric disturbance in Alzheimer's disease. *Int J Geriatr Psychiatry* 2001;16:1037-42.
34. Lyketsos CG, Lopez O, Jones B, et al. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 2002;288:1475-83.
35. Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Environmental correlates of neuropsychiatric symptoms in nursing home patients with dementia. *Int J Geriatr Psychiatry* 2010;25:14-22.
36. Scholzel-Dorenbos CJ, Meeuwssen EJ, Olde Rikkert MG. Integrating unmet needs into dementia health-related quality of life research and care: introduction of the Hierarchy Model of Needs in Dementia. *Aging Ment Health* 2010;14:113-9.
37. Sampson EL, White N, Lord K, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study. *Pain* 2015;156:675-83.

38. Husebo BS, Ballard C, Sandvik R, et al. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ* 2011;343:d4065.
39. Husebo BS, Ballard C, Fritze F, et al. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. *Int J Geriatr Psychiatry* 2014;29:828-36.
40. Kim SK, Park M. Effectiveness of person-centered care on people with dementia: a systematic review and meta-analysis. *Clin Interv Aging* 2017;12:381-97.
41. Brailean A, Comijs HC, Aartsen MJ, et al. Late-life depression symptom dimensions and cognitive functioning in the Longitudinal Aging Study Amsterdam (LASA). *J Affect Disord* 2016;201:171-8.
42. Butters MA, Whyte EM, Nebes RD, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry* 2004;61:587-95.
43. Sheline YI, Barch DM, Garcia K, et al. Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biol Psychiatry* 2006;60:58-65.
44. Koenig AM, Bhalla RK, Butters MA. Cognitive functioning and late-life depression. *J Int Neuropsychol Soc* 2014;20:461-7.
45. Bhalla RK, Butters MA, Mulsant BH, et al. Persistence of neuropsychologic deficits in the remitted state of late-life depression. *Am J Geriatr Psychiatry* 2006;14:419-27.
46. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord* 2011;134:20-31.
47. Barch DM, D'Angelo G, Pieper C, et al. Cognitive improvement following treatment in late-life depression: relationship to vascular risk and age of onset. *Am J Geriatr Psychiatry* 2012;20:682-90.
48. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord* 2016;190:264-71.
49. Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. *Curr Opin Psychiatry* 2011;24:461-72.
50. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. *Am J Geriatr Psychiatry* 2002;10:125-8.
51. Selbaek G, Engedal K. Stability of the factor structure of the Neuropsychiatric Inventory in a 31-month follow-up study of a large sample of nursing-home patients with dementia. *Int Psychogeriatr* 2012;24:62-73.
52. Selbaek G, Engedal K, Bergh S. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. *J Am Med Dir Assoc* 2013;14:161-9.
53. Borza T, Engedal K, Bergh S, et al. The course of depressive symptoms as measured by the Cornell scale for depression in dementia over 74 months in 1158 nursing home residents. *J Affect Disord* 2014;175:209-16.
54. Goodarzi ZS, Mele BS, Roberts DJ, Holroyd-Leduc J. Depression case finding in individuals with dementia: a systematic review and meta-analysis. *J Am Geriatr Soc* 2017;65:937-48.
55. Gonzalez-Salvador T, Lyketsos CG, Baker A, et al. Quality of life in dementia patients in long-term care. *Int J Geriatr Psychiatry* 2000;15:181-9.
56. Potter GG, Steffens DC. Contribution of depression to cognitive impairment and dementia in older adults. *Neurologist* 2007;13:105-17.

57. Rapp MA, Schnaider-Beeri M, Wysocki M, et al. Cognitive decline in patients with dementia as a function of depression. *Am J Geriatr Psychiatry* 2011;19:357-63.
58. Bellelli G, Frisoni GB, Turco R, Trabucchi M. Depressive symptoms combined with dementia affect 12-months survival in elderly patients after rehabilitation post-hip fracture surgery. *Int J Geriatr Psychiatry* 2008;23:1073-7.
59. Lenze EJ, Skidmore ER, Dew MA, et al. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen Hosp Psychiatry* 2007;29:141-6.
60. Smith TO, Hameed YA, Cross JL, et al. Enhanced rehabilitation and care models for adults with dementia following hip fracture surgery. *Cochrane Database Syst Rev* 2015:CD010569.
61. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: a review. *Int J Geriatr Psychiatry* 2013;28:1109-24.
62. Janzing JG, Bouwens JM, Teunisse RJ, et al. The relationship between depression and mortality in elderly subjects with less severe dementia. *Psychol Med* 1999;29:979-83.
63. The Norwegian Directorate of Health (Helsedirektoratet). Nasjonal faglig retningslinje om demens IS-2658. Published 18.08.2017.
64. Goodarzi Z, Mele B, Guo S, et al. Guidelines for dementia or Parkinson's disease with depression or anxiety: a systematic review. *BMC Neurol* 2016;16:244.
65. Rabins PV, Blacker D, Rovner BW, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007;164:5-56.
66. Lyketsos CG, DelCampo L, Steinberg M, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry* 2003;60:737-46.
67. Rosenberg PB, Drye LT, Martin BK, et al. Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry* 2010;18:136-45.
68. Reifler BV, Teri L, Raskind M, et al. Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. *Am J Psychiatry* 1989;146:45-9.
69. Petracca G, Teson A, Chemerinski E, et al. A double-blind placebo-controlled study of clomipramine in depressed patients with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 1996;8:270-5.
70. Roth M, Mountjoy CQ, Amrein R. Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. *Br J Psychiatry* 1996;168:149-57.
71. Magai C, Kennedy G, Cohen CI, Gomberg D. A controlled clinical trial of sertraline in the treatment of depression in nursing home patients with late-stage Alzheimer's disease. *Am J Geriatr Psychiatry* 2000;8:66-74.
72. Petracca GM, Chemerinski E, Starkstein SE. A double-blind, placebo-controlled study of fluoxetine in depressed patients with Alzheimer's disease. *Int Psychogeriatr* 2001;13:233-40.
73. de Vasconcelos Cunha UG, Lopes Rocha F, Avila de Melo R, et al. A placebo-controlled double-blind randomized study of venlafaxine in the treatment of depression in dementia. *Dement Geriatr Cogn Disord* 2007;24:36-41.
74. Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 2011;378:403-11.
75. Bains J, Birks J, Denning T. Antidepressants for treating depression in dementia. *Cochrane Database Syst Rev* 2002:CD003944.

- 
76. Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J Am Geriatr Soc* 2011;59:577-85.
  77. Leong C. Antidepressants for depression in patients with dementia: a review of the literature. *Consult Pharm* 2014;29:254-63.
  78. Weintraub D, Rosenberg PB, Drye LT, et al. Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. *Am J Geriatr Psychiatry* 2010;18:332-40.
  79. Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551.
  80. Bakken MS, Engeland A, Engesaeter LB, et al. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. *Age Ageing* 2013;42:514-20.
  81. Mueller C, Huntley J, Stubbs B, et al. Associations of neuropsychiatric symptoms and antidepressant prescription with survival in Alzheimer's disease. *J Am Med Dir Assoc* 2017;18:1076-81.
  82. Gulla C, Selbaek G, Flo E, et al. Multi-psychotropic drug prescription and the association to neuropsychiatric symptoms in three Norwegian nursing home cohorts between 2004 and 2011. *BMC Geriatr* 2016;16:115.
  83. Janus SI, van Manen JG, IJzerman MJ, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *Int Psychogeriatr* 2016;28:1775-90.
  84. Testad I, Corbett A, Aarsland D, et al. The value of personalized psychosocial interventions to address behavioral and psychological symptoms in people with dementia living in care home settings: a systematic review. *Int Psychogeriatr* 2014;26:1083-98.
  85. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ* 2015;350:h369.
  86. Orgeta V, Qazi A, Spector A, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *Br J Psychiatry* 2015;207:293-8.
  87. Kales HC, Gitlin LN, Lyketsos CG, et al. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc* 2014;62:762-9.
  88. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol* 2009;5:245-55.
  89. Bonica JJ. The need of a taxonomy. *Pain* 1979;6:247-8.
  90. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;6:249.
  91. Defrin R, Amanzio M, de Tommaso M, et al. Experimental pain processing in individuals with cognitive impairment: current state of the science. *Pain* 2015;156:1396-408.
  92. Anand KJ, Craig KD. New perspectives on the definition of pain. *Pain* 1996;67:3-6.
  93. Hadjistavropoulos T (Ed.), Craig KD (Ed.). Pain: Psychological perspectives. 1<sup>st</sup> edn. New York: Psychology Press 2004.
  94. Pautex S, Michon A, Guedira M, et al. Pain in severe dementia: self-assessment or observational scales? *J Am Geriatr Soc* 2006;54:1040-5.
  95. Corbett A, Husebo B, Malcangio M, et al. Assessment and treatment of pain in people with dementia. *Nat Rev Neurol* 2012;8:264-74.

96. Husebo BS, Strand LI, Moe-Nilssen R, et al. Who suffers most? Dementia and pain in nursing home patients: a cross-sectional study. *J Am Med Dir Assoc* 2008;9:427-33.
97. Rostad HM, Puts MTE, Cvancarova Smastuen M, et al. Associations between pain and quality of life in severe dementia: a Norwegian cross-sectional study. *Dement Geriatr Cogn Dis Extra* 2017;7:109-21.
98. Landmark BT, Gran SV, Kim HS. Pain and persistent pain in nursing home residents in Norway. *Res Gerontol Nurs* 2013;6:47-56.
99. Tan EC, Jokanovic N, Koponen MP, et al. Prevalence of analgesic use and pain in people with and without dementia or cognitive impairment in aged care facilities: a systematic review and meta-analysis. *Curr Clin Pharmacol* 2015;10:194-203.
100. Sieber FE, Mears S, Lee H, Gottschalk A. Postoperative opioid consumption and its relationship to cognitive function in older adults with hip fracture. *J Am Geriatr Soc* 2011;59:2256-62.
101. Achterberg WP, Pieper MJ, van Dalen-Kok AH, et al. Pain management in patients with dementia. *Clin Interv Aging* 2013;8:1471-82.
102. Rainero I, Vighetti S, Bergamasco B, et al. Autonomic responses and pain perception in Alzheimer's disease. *Eur J Pain* 2000;4:267-74.
103. Corbett A, Husebo BS, Achterberg WP, et al. The importance of pain management in older people with dementia. *Br Med Bull* 2014;111:139-48.
104. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease - lessons from pathology. *BMC Medicine* 2014;12:206.
105. Scherder EJ, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. *Lancet Neurol* 2003;2:677-86.
106. Sandvik R, Selbaek G, Kirkevold O, et al. Analgesic prescribing patterns in Norwegian nursing homes from 2000 to 2011: trend analyses of four data samples. *Age Ageing* 2016;45:54-60.
107. Tan EC, Visvanathan R, Hilmer SN, et al. Analgesic use and pain in residents with and without dementia in aged care facilities: A cross-sectional study. *Australas J Ageing* 2016;35:180-7.
108. Jensen-Dahm C, Gasse C, Astrup A, et al. Frequent use of opioids in patients with dementia and nursing home residents: a study of the entire elderly population of Denmark. *Alzheimers Dement* 2015;11:691-9.
109. Bauer U, Pitzer S, Schreier MM, et al. Pain treatment for nursing home residents differs according to cognitive state – a cross-sectional study. *BMC Geriatr* 2016;16:124.
110. Vandraas KF, Spigset O, Mahic M, Slordal L. Non-steroidal anti-inflammatory drugs: use and co-treatment with potentially interacting medications in the elderly. *Eur J Clin Pharmacol* 2010;66:823-9.
111. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8.
112. Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Ther* 2005;12:46-55.
113. Graham GG, Davies MJ, Day RO, et al. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013;21:201-32.
114. Pathan H, Williams J. Basic opioid pharmacology: an update. *Br J Pain* 2012;6:11-6.
115. Holzer P. Opioid receptors in the gastrointestinal tract. *Regul Pept* 2009;155:11-7.
116. Lehnen N, Heuser F, Sağlam M, et al. Opioid-induced nausea involves a vestibular problem preventable by head-rest. *PLoS ONE* 2015;10:e0135263.

117. Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. *Br J Pharmacol* 2011;164:1322-34.
118. Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* 2008;100:747-58.
119. Pick CG, Peter Y, Schreiber S, Weizman R. Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with kappa 3 analgesia. *Brain Res* 1997;744:41-6.
120. Lutfy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. *Curr Neuropharmacol* 2004;2:395-402.
121. Pergolizzi J, Aloisi AM, Dahan A, et al. Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract* 2010;10:428-50.
122. Vadivelu N, Hines RL. Management of chronic pain in the elderly: focus on transdermal buprenorphine. *Clin Interv Aging* 2008;3:421-30.
123. Likar R. Transdermal buprenorphine in the management of persistent pain – safety aspects. *Ther Clin Risk Manag* 2006;2:115-25.
124. Kaestli LZ, Wasilewski-Rasca AF, Bonnabry P, Vogt-Ferrier N. Use of transdermal drug formulations in the elderly. *Drugs Aging* 2008;25:269-80.
125. Khanna IK, Pillarsetti S. Buprenorphine – an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res* 2015;8:859-70.
126. Husebo BS, Achterberg W, Flo E. Identifying and managing pain in people with Alzheimer's disease and other types of dementia: a systematic review. *CNS Drugs* 2016;30:481-97.
127. Buffum MD, Sands L, Miaskowski C, et al. A clinical trial of the effectiveness of regularly scheduled versus as-needed administration of acetaminophen in the management of discomfort in older adults with dementia. *J Am Geriatr Soc* 2004;52:1093-7.
128. Hurley AC, Volicer BJ, Hanrahan PA, et al. Assessment of discomfort in advanced Alzheimer patients. *Res Nurs Health* 1992;15:369-77.
129. Chibnall JT, Tait RC, Harman B, Luebbert RA. Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia. *J Am Geriatr Soc* 2005;53:1921-9.
130. Manfredi PL, Breuer B, Wallenstein S, et al. Opioid treatment for agitation in patients with advanced dementia. *Int J Geriatr Psychiatry* 2003;18:700-5.
131. Kalso E. Oxycodone. *J Pain Symptom Manage* 2005;29(5 Suppl):S47-56.
132. Miller M, Sturmer T, Azrael D, et al. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc* 2011;59:430-8.
133. Blake H, Leighton P, van der Walt G, Ravenscroft A. Prescribing opioid analgesics for chronic non-malignant pain in general practice - a survey of attitudes and practice. *Br J Pain* 2015;9:225-32.
134. American Geriatrics Society. The management of chronic pain in older persons: AGS Panel on Chronic Pain in Older Persons. *J Am Geriatr Soc* 1998;46:635-51.
135. Buffum MD, Miaskowski C, Sands L, Brod M. A pilot study of the relationship between discomfort and agitation in patients with dementia. *Geriatr Nurs* 2001;22:80-5.
136. Cohen-Mansfield J, Dakheel-Ali M, Marx MS, et al. Which unmet needs contribute to behavior problems in persons with advanced dementia? *Psychiatry Res* 2015;228:59-64.
137. Regier NG, Gitlin LN. Dementia-related restlessness: relationship to characteristics of persons with dementia and family caregivers. *Int J Geriatr Psychiatry* 2018;33:185-92.

138. Husebo BS, Ballard C, Aarsland D. Pain treatment of agitation in patients with dementia: a systematic review. *Int J Geriatr Psychiatry* 2011;26:1012-8.
139. Pieper MJ, van Dalen-Kok AH, Francke AL, et al. Interventions targeting pain or behaviour in dementia: a systematic review. *Ageing Res Rev* 2013;12:1042-55.
140. Tampi RR, Hassell C, Joshi P, Tampi DJ. Analgesics in the management of behavioral and psychological symptoms of dementia: a perspective review. *Drugs Context* 2017;6:212508.
141. Woo C-W, Wager TD. Neuroimaging-based biomarker discovery and validation. *Pain* 2015;156:1379-81.
142. Goldenberg DL. Pain/Depression dyad: a key to a better understanding and treatment of functional somatic syndromes. *Am J Med* 2010;123:675-82.
143. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433-45.
144. Chopra K, Arora V. An intricate relationship between pain and depression: clinical correlates, coactivation factors and therapeutic targets. *Expert Opin Ther Targets* 2014;18:159-76.
145. Cipher DJ, Clifford PA. Dementia, pain, depression, behavioral disturbances, and ADLs: toward a comprehensive conceptualization of quality of life in long-term care. *Int J Geriatr Psychiatry* 2004;19:741-8.
146. Williams CS, Zimmerman S, Sloane PD, Reed PS. Characteristics associated with pain in long-term care residents with dementia. *Gerontologist* 2005;45:68-73.
147. Leong IY, Nuo TH. Prevalence of pain in nursing home residents with different cognitive and communicative abilities. *Clin J Pain* 2007;23:119-27.
148. Malara A, De Biase GA, Bettarini F, et al. Pain assessment in elderly with behavioral and psychological symptoms of dementia. *J Alzheimers Dis* 2016;50:1217-25.
149. Gruber-Baldini AL, Zimmerman S, Boustani M, et al. Characteristics associated with depression in long-term care residents with dementia. *Gerontologist* 2005;45:50-5.
150. Debruyne H, Van Buggenhout M, Le Bastard N, et al. Is the geriatric depression scale a reliable screening tool for depressive symptoms in elderly patients with cognitive impairment? *Int J Geriatr Psychiatry* 2009;24:556-62.
151. Hadjistavropoulos T, Herr K, Prkachin KM, et al. Pain assessment in elderly adults with dementia. *Lancet Neurol* 2014;13:1216-27.
152. van Dalen-Kok AH, Pieper MJ, de Waal MW, et al. Association between pain, neuropsychiatric symptoms, and physical function in dementia: a systematic review and meta-analysis. *BMC Geriatr* 2015;15:49.
153. Reisberg B. Functional assessment staging (FAST). *Psychopharmacol Bull* 1988;24:653-9.
154. Cohen-Mansfield J, Libin A. Assessment of agitation in elderly patients with dementia: correlations between informant rating and direct observation. *Int J Geriatr Psychiatry* 2004;19:881-91.
155. Sandvik RK, Selbaek G, Seifert R, et al. Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: A cluster randomized trial. *Eur J Pain* 2014;18:1490-500.
156. Simonin F, Gavériaux-Ruff C, Befort K, et al. kappa-Opioid receptor in humans: cDNA and genomic cloning, chromosomal assignment, functional expression, pharmacology, and expression pattern in the central nervous system. *Proc Natl Acad Sci U S A* 1995;92:7006-10.
157. Knoll AT, Carlezon WA. Dynorphin, stress, and depression. *Brain Res* 2010;1314:56-73.



158. Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. *Science* 1986;233:774-6.
159. Mague SD, Pliakas AM, Todtenkopf MS, et al. Antidepressant-like effects of kappa-opioid receptor antagonists in the forced swim test in rats. *J Pharmacol Exp Ther* 2003;305:323-30.
160. Carroll FI, Carlezon WA. Development of kappa opioid receptor antagonists. *J Med Chem* 2013;56:2178-95.
161. Shippenberg TS. The dynorphin/kappa opioid receptor system: a new target for the treatment of addiction and affective disorders? *Neuropsychopharmacology* 2009;34:247.
162. Emrich HM, Vogt P, Herz A. Possible antidepressive effects of opioids: action of buprenorphine. *Ann N Y Acad Sci* 1982;398:108-12.
163. Karp JF, Butters MA, Begley AE, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. *J Clin Psychiatry* 2014;75:e785-93.
164. Garay RP, Zarate CA, Charpeaud T, et al. Investigational drugs in recent clinical trials for treatment-resistant depression. *Expert Rev Neurother* 2017;17:593-609.
165. Fava M, Memisoglu A, Thase ME, et al. Opioid modulation with buprenorphine/samidorphane as adjunctive treatment for inadequate response to antidepressants: a randomized double-blind placebo-controlled trial. *Am J Psychiatry* 2016;173:499-508.
166. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
167. Pernecky R, Wagenpfeil S, Komossa K, et al. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry* 2006;14:139-44.
168. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* 1992;40:922-35.
169. Husebo BS, Strand LI, Moe-Nilssen R, et al. Pain behaviour and pain intensity in older persons with severe dementia: reliability of the MOBID Pain Scale by video uptake. *Scand J Caring Sci* 2009;23:180-9.
170. Husebo BS, Strand LI, Moe-Nilssen R, et al. Pain in older persons with severe dementia. Psychometric properties of the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale in a clinical setting. *Scand J Caring Sci* 2010;24:380-91.
171. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. *Eur J Pain* 2014;18:1419-30.
172. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. *Biol Psychiatry* 1988;23:271-84.
173. Korner A, Lauritzen L, Abelskov K, et al. The Geriatric Depression Scale and the Cornell Scale for Depression in Dementia. A validity study. *Nord J Psychiatry* 2006;60:360-4.
174. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS ONE* 2012;7:e39198.
175. Lambiase MJ, Gabriel KP, Chang YF, et al. Utility of actiwatch sleep monitor to assess waking movement behavior in older women. *Med Sci Sports Exerc* 2014;46:2301-7.

176. Creavin ST, Wisniewski S, Noel-Storr AH, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev* 2016:CD011145.
177. Tsoi KK, Chan JY, Hirai HW, et al. Cognitive tests to detect dementia: a systematic review and meta-analysis. *JAMA Intern Med* 2015;175:1450-8.
178. Barca ML, Engedal K, Selbaek G, et al. Confirmatory factor analysis of the Cornell Scale for Depression in Dementia among patient with dementia of various degrees. *J Affect Disord* 2015;188:173-8.
179. Lai CKY. The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. *Clin Interv Aging* 2014;9:1051-61.
180. Aalten P, de Vugt ME, Lousberg R, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cogn Disord* 2003;15:99-105.
181. Hollingworth P, Hamshere ML, Moskvina V, et al. Four components describe behavioral symptoms in 1,120 individuals with late-onset Alzheimer's disease. *J Am Geriatr Soc* 2006;54:1348-54.
182. Cheng ST, Kwok T, Lam LC. Neuropsychiatric symptom clusters of Alzheimer's disease in Hong Kong Chinese: prevalence and confirmatory factor analysis of the Neuropsychiatric Inventory. *Int Psychogeriatr* 2012;24:1465-73.
183. Selbaek G, Engedal K. Stability of the factor structure of the Neuropsychiatric Inventory in a 31-month follow-up study of a large sample of nursing-home patients with dementia. *Int Psychogeriatr* 2012;24:62-73.
184. Boustani M, Campbell N, Munger S, et al. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health* 2008;4:311-20.
185. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr* 2015;15:31.
186. Husebo BS, Flo E, Aarsland D, et al. COSMOS--improving the quality of life in nursing home patients: protocol for an effectiveness-implementation cluster randomized clinical hybrid trial. *Implement Sci* 2015;10:131.
187. Bailey C, Peddie D, Wickham ME, et al. Adverse drug event reporting systems: a systematic review. *Br J Clin Pharmacol* 2016;82:17-29.
188. Crisp A. Blinding in pharmaceutical clinical trials: An overview of points to consider. *Contemp Clin Trials* 2015;43:155-63.
189. Guthrie B, Payne K, Alderson P, et al. Adapting clinical guidelines to take account of multimorbidity. *BMJ* 2012;345:e6341.
190. Snow AL, Cook KF, Lin P-S, et al. Proxies and other external raters: methodological considerations. *Health Services Research* 2005;40:1676-93.
191. Schulz R, Cook TB, Beach SR, et al. Magnitude and causes of bias among family caregivers rating Alzheimer's disease patients. *Am J Geriatr Psychiatry* 2013;21:14-25.
192. Arons AMM, Krabbe PFM, Schölzel-Dorenbos CJM, et al. Quality of life in dementia: a study on proxy bias. *BMC Med Res Methodol* 2013;13:110.
193. Orgeta V, Orrell M, Edwards RT, et al. Self- and carer-rated pain in people with dementia: influences of pain in carers. *J Pain Symptom Manage* 2015;49:1042-9.
194. Leung VP, Lam LC, Chiu HF, et al. Validation study of the Chinese version of the neuropsychiatric inventory (CNPI). *Int J Geriatr Psychiatry* 2001;16:789-93.

195. Selbaek G, Kirkevold O, Sommer OH, Engedal K. The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, nursing home version (NPI-NH). *Int Psychogeriatr* 2008;20:375-82.
196. Lichtner V, Dowding D, Esterhuizen P, et al. Pain assessment for people with dementia: a systematic review of systematic reviews of pain assessment tools. *BMC Geriatr* 2014;14:138.
197. Woo A, Lechner B, Fu T, et al. Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: a literature review. *Ann Palliat Med* 2015;4:176-83.
198. Hirschfeld G, Zernikow B. Variability of "optimal" cut points for mild, moderate, and severe pain: neglected problems when comparing groups. *Pain* 2013;154:154-9.
199. Wertli MM, Burgstaller JM, Weiser S, et al. Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review. *Spine* 2014;39:263-73.
200. Boonstra AM, Stewart RE, Köke AJA, et al. Cut-off points for mild, moderate, and severe pain on the Numeric Rating Scale for pain in patients with chronic musculoskeletal pain: variability and influence of sex and catastrophizing. *Front Psychol* 2016;7:1466.
201. Nygaard HA, Ruths S. Missing the diagnosis: senile dementia in patients admitted to nursing homes. *Scand J Prim Health Care* 2003;21:148-52.
202. Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. *BMJ Open* 2017;7:e011146.
203. Karantzoulis S, Galvin JE. Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Rev Neurother* 2011;11:1579-91.
204. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;69:2197-204.
205. Ritchie CW, Terrera GM, Quinn TJ. Dementia trials and dementia tribulations: methodological and analytical challenges in dementia research. *Alzheimers Res Ther* 2015;7:31.
206. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol* 2014;67:267-77.
207. Nichols AL, Maner JK. The good-subject effect: investigating participant demand characteristics. *J Gen Psychol* 2008;135:151-65.
208. Linde K, Witt CM, Streng A, et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* 2007;128:264-71.
209. Thompson C. If you could just provide me with a sample: examining sampling in qualitative and quantitative research papers. *Evidence Based Nursing* 1999;2:68.
210. Markovic G, Schult ML, Bartfai A. The effect of sampling bias on generalizability in intervention trials after brain injury. *Brain Inj* 2017;31:9-15.
211. Erdal A, Flo E, Selbaek G, et al. Associations between pain and depression in nursing home patients at different stages of dementia. *J Affect Disord* 2017;218:8-14.
212. Robards J, Evandrou M, Falkingham J, Vlachantoni A. Mortality at older ages and moves in residential and sheltered housing: evidence from the UK. *J Epidemiol Community Health* 2014;68:524-9.
213. Husebo BS, Ballard C, Cohen-Mansfield J, et al. The response of agitated behavior to pain management in persons with dementia. *Am J Geriatr Psychiatry* 2014;22:708-17.

- 
214. Conaghan PG, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. *Osteoarthritis Cartilage* 2011;19:930-8.
  215. Gianni W, Madaio AR, Ceci M, et al. Transdermal buprenorphine for the treatment of chronic noncancer pain in the oldest old. *J Pain Symptom Manage* 2011;41:707-14.
  216. Karlsson J, Soderstrom A, Augustini BG, Berggren AC. Is buprenorphine transdermal patch equally safe and effective in younger and elderly patients with osteoarthritis-related pain? Results of an age-group controlled study. *Curr Med Res Opin* 2014;30:575-87.
  217. Likar R, Vadlau EM, Breschan C, et al. Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. *Clin J Pain* 2008;24:536-43.
  218. Muriel C, Perez-Castejon Garrote JM, Sanchez Magro I, Neira Alvarez M. [Effectiveness and safety of transdermal buprenorphine for chronic pain treatment in the elderly: a prospective observational study]. *Med Clin (Barc)* 2007;128:204-10.
  219. Pergolizzi JV, Raffa RB, Marcum Z, et al. Safety of buprenorphine transdermal system in the management of pain in older adults. *Postgrad Med* 2017;129:92-101.
  220. Kanagaratnam L, Drame M, Trenque T, et al. Adverse drug reactions in elderly patients with cognitive disorders: a systematic review. *Maturitas* 2016;85:56-63.
  221. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging* 2014;9:2079-86.
  222. James BD, Boyle PA, Bennett DA, Buchman AS. Total Daily Activity measured with actigraphy and motor function in community-dwelling older persons with and without dementia. *Alzheimer Dis Assoc Disord* 2012;26:238-45.
  223. Huisingh-Scheetz M, Wroblewski K, Kocherginsky M, et al. The relationship between physical activity and frailty among U.S. older adults based on hourly accelerometry data. *J Gerontol A Biol Sci Med Sci* 2018;73:622-9.
  224. Llamas-Velasco S, Villarejo-Galende A, Contador I, et al. Physical activity and long-term mortality risk in older adults: a prospective population based study (NEDICES). *Prev Med Rep* 2016;4:546-50.
  225. van Alphen HJM, Volkers KM, Blankevoort CG, et al. Older adults with dementia are sedentary for most of the day. *PLoS ONE* 2016;11:e0152457.
  226. Gillman PK. A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action. *Biol Psychiatry* 2006;59:1046-51.
  227. Cipriani A, La Ferla T, Furukawa TA, et al. Sertraline versus other antidepressive agents for depression. *Cochrane Database Syst Rev* 2009;Cd006117.
  228. Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? *Int Clin Psychopharmacol* 2014;29:185-96.
  229. Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. *CNS Drug Rev* 2001;7:249-64.
  230. Westenberg HG. Pharmacology of antidepressants: selectivity or multiplicity? *J Clin Psychiatry* 1999;60 Suppl 17:4-8; discussion 46-8.
  231. Lalanne L, Ayranci G, Kieffer BL, Lutz P-E. The kappa opioid receptor: from addiction to depression, and back. *Front Psychiatry* 2014;5:170.
  232. Sundaramurthy S, Annamalai B, Samuvel DJ, et al. Modulation of serotonin transporter function by kappa-opioid receptor ligands. *Neuropharmacology* 2017;113:281-92.

233. Kivell B, Uzelac Z, Sundaramurthy S, et al. Salvinorin A regulates dopamine transporter function via a kappa opioid receptor and ERK1/2-dependent mechanism. *Neuropharmacology* 2014;86:228-40.
234. Isenberg D, Wong SC, Curtis JA. Serotonin syndrome triggered by a single dose of suboxone. *Am J Emerg Med* 2008;26:840.e3-840.e5.
235. Jhun P, Bright A, Herbert M. Serotonin syndrome and opioids—what’s the deal? *Ann Emerg Med* 2015;65:434-5.
236. Gnanadesigan N, Espinoza RT, Smith R, et al. Interaction of serotonergic antidepressants and opioid analgesics: is serotonin syndrome going undetected? *J Am Med Dir Assoc* 2005;6:265-9.
237. Hilmer SN, Gnjdic D. Prescribing for frail older people. *Aust Prescr* 2017;40:174-8.
238. Buffel du Vaure C, Dechartres A, Battin C, et al. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: a systematic review of registration details. *BMJ Open* 2016;6:e012265.
239. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-4.

## Appendix I

## MMSE-NR

TL starter med følgende spørsmål: **Synes du hukommelsen har blitt dårligere?** Ja  Nei  Vet ikke   
**Jeg skal nå stille deg noen spørsmål, som vi spør alle om. Svar så godt du kan.**  
Instruksjon kan gjentas, unntatt på oppg. 12 og 17.

### TIDSORIENTERING

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

### STEDSORIENTERING

På spørsmål 7 brukes "Landsdel" ved testing i Oslo, "Fylke" utenfor Oslo.  
Sett ring rundt valgt stedsord for spørsmål 8 og 9.

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

### UMIDDELBAR GJENKALLING/REGISTRERING

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

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

Dersom pasienten ikke gjentar alle 3 ord, repeteres alle ord inntil alle gjengis i samme forsøk, maks. 3 presentasjoner. Det gis kun poeng etter 1. presentasjon, rekkefølge pasienten sier ordene er uten betydning.

Antall presentasjoner: \_\_\_\_\_stk.

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

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

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

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

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

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

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

\*\*Eventuell distraksjonsbetingelse – OBS, er ikke poenggivende!

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

## UTSATT GJENKALLING

Poeng

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

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

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

## BENEVNING

14. Hva heter dette? [Pek på en blyant] -----  0  115. Hva heter dette? [Pek på et armbåndsur] -----  0  1

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

## REPETISJON

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

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

Antall presentasjoner: \_\_\_\_\_ stk.

## FORSTÅELSE

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

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

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

## LESNING

18. Nå vil jeg at du gjør det som står på arket [Vis pasienten teksten].

Pasienten må lukke øynene for poeng.

LUKK ØYNENE DINE -----  0  1

## SKRIVNING/SETNINGSGENERERING

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

19. Skriv en meningsfull setning her [Pek på øvre del av side 4].

Skriver ikke pasienten noe, si: **Skriv om været.** -----  0  1

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

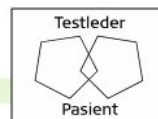
Setningen må være forståelig, men trenger ikke inneholde objekt. Se eksempler i manual\*. Det gis poeng ved riktig utførelse selv etter supplerende instruksjon. Ignorer stave- og grammatikalske feil.

## TEGNING/FIGURKOPIERING

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

20. Kopier figuren så nøyaktig du kan her [Pek på nedre del av side 4].

Du kan bruke viskelær. Ta deg god tid. Si fra når du er ferdig.

 0  1

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

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

TOTAL POENGSUM = \_\_\_\_/30. Presiser hva pasienten hadde utfall (feilsvar) på:

\_\_\_\_\_

\_\_\_\_\_



# Mobid-2 smerteskala

Mobilisation – Observation – Behaviour – Intensity – Dementia

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



**Smertelyd**  
«Aul»  
Stenner  
Ynker seg  
Gisper  
Skriker



**Ansiktsuttrykk**  
Grimaserer  
Rynker pannen  
Strammer munnen  
Lukker øynene



**Avvergereaksjon**  
Støtver  
Beskytter seg  
Skryter fra seg  
Endringer i pusten  
Krymper seg

1. Led til å åpne begge hender

2. Led til å strekke armene mot hodet

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

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

5. Led til å sette seg opp på sengekanten

## SMERTEINTENSITET

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

0 er ingen smerte, 10 er verst tenkelig smerte

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

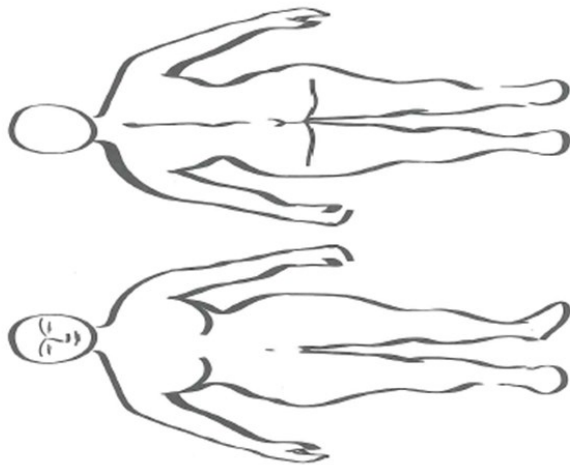
0 1 2 3 4 5 6 7 8 9 10

0 1 2 3 4 5 6 7 8 9 10

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

## SMERTEATFERD

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



6. Hode, munn, hals

7. Bryst, lunge, hjerte

8. Mage – øvre del

9. Bekken, mage – nedre del

10. Hud, infeksjon, sår

## SMERTEINTENSITET

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

0 er ingen smerte, 10 er verst tenkelig smerte



Gi en helhetlig vurdering av pasientens smerteintensitet basert på alle observasjoner



# Cornell – skala for depresjon

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

Pasientens navn: \_\_\_\_\_ Dato for utredning: \_\_\_\_\_

Utfylt av: \_\_\_\_\_

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

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

## Svaralternativ

a. Lar seg ikke evaluere

0. Ikke til stede

1. Moderat eller bare  
periodevis til stede

2. Mye til stede

a 0 1 2

### A: Stemningssymptomer

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

### B: Forstyrret atferd

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

### C: Kroppslige uttrykk

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

### D: Døgnvariasjoner

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

### E: Tankeforstyrrelser

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

Cornell sum skåre

## NPI-NH

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

### Hypighet - hvor ofte skjer adferden?

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

### Intensitet – hvor ille er det for pasienten?

1. Mild - medfører liten belastning for beboeren
2. Moderat - forårsaker uvanlig eller merkelig atferd
3. Alvorlig - forstyrrende og forårsaker mye uvanlig eller merkelig atferd

### Belastning – hvor mye merarbeid er det for pleierne?

0. Ikke i det hele tatt
1. Minimalt
2. Mild
3. Moderat
4. Alvorlig
5. Svært alvorlig eller ekstremt

### **1. Vrangforestillinger**

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

### **2. Hallusinasjoner**

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

### **3. Agitasjon/agresjon**

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

### **4. Depresjon/dysfori**

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

### **5. Angst**

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

### **6. Oppstemthet/Eufori**

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

### **7. Apati/Likegyldighet**

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

### **8. Manglende hemning**

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

### **9. Irritabilitet/Labilitet**

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

### **10. Avvikende motorisk atferd**

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

### **11. Søvn**

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

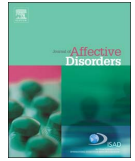
### **12. Appetitt- eller spiseforstyrrelser**

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

---

**Paper I**

**I**



## Research paper

## Associations between pain and depression in nursing home patients at different stages of dementia



Ane Erdal<sup>a,\*</sup>, Elisabeth Flo<sup>a,b</sup>, Geir Selbaek<sup>c,d,e</sup>, Dag Aarsland<sup>f,g</sup>, Sverre Bergh<sup>c,d</sup>,  
Dagrun D. Slettebo<sup>a</sup>, Bettina S. Husebo<sup>a,h</sup>

<sup>a</sup> Department of Global Public Health and Primary Care, Centre for Elderly and Nursing Home Medicine, University of Bergen, Bergen, Norway

<sup>b</sup> Department of Clinical Psychology, University of Bergen, Bergen, Norway

<sup>c</sup> Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, Ottestad, Norway

<sup>d</sup> National Advisory Unit on Ageing and Health, Tønsberg, Norway

<sup>e</sup> Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>f</sup> Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

<sup>g</sup> Centre for Age-related Medicine, Stavanger University Hospital, Stavanger, Norway

<sup>h</sup> Municipality of Bergen, Bergen, Norway

## ARTICLE INFO

## Keywords:

Depression  
Pain  
Dementia  
Nursing home

## ABSTRACT

**Background:** Pain is associated with depression in nursing home patients with dementia. It is, however, unclear whether pain increases depression. Therefore we evaluated the prospective associations between pain and depressive symptoms in nursing home patients at different stages of cognitive impairment.

**Methods:** Two longitudinal studies were combined, including 931 patients ( $\geq 65$  years) from 65 nursing homes. One study assessed patients at admission, with 6-month follow-up (2012–2014). The other study assessed residents with varying lengths of stay, with 4-month follow-up (2014–2015). Patients were assessed with the Mini-Mental State Examination, the Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, and the Cornell Scale for Depression in Dementia.

**Results:** At baseline, 343 patients (40% of 858 assessed) had moderate to severe pain, and 347 (38% of 924) had depression. Pain increased the risk of depression (OR 2.35, 95% CI 1.76–3.12). Using mixed model analyses, we found that a 1-point increase in pain was associated with a .48 increase in depression ( $p < .001$ ). This association persisted in mild, moderate, and severe cognitive impairment. In those recently admitted, depressive symptoms decreased over time, and having less pain at follow-up was associated with a decrease in depressive symptoms (within-subject effect;  $p = .042$ ).

**Limitations:** The two cohorts had different inclusion criteria, which may reduce generalisability. The study design does not allow conclusions on causality.

**Conclusions:** Pain and depressive symptoms are associated in patients with dementia. Because reduced pain is associated with less depressive symptoms, these patients should be assessed regularly for untreated pain. The benefit of analgesic treatment should be weighed carefully against the potential for adverse effects.

## 1. Introduction

In Norway, over 80% of nursing home patients have dementia (Helvik et al., 2015). Symptoms of depression affect up to 50% of people with dementia, causing increased suffering, reduced quality of life, and possibly shortened life expectancy (Enache et al., 2011; Gonzalez-Salvador et al., 2000; Janzing et al., 1999; Todd et al., 2013). Depression in people with dementia may also accelerate the decline in daily functioning and cognition, and contribute to the loss of independence and earlier nursing home placement (Luppa et al., 2008;

Potter and Steffens, 2007; Rapp et al., 2011). Over time, depression often persists and re-occurs in these individuals (Selbaek and Engedal, 2012; Selbaek et al., 2013), and may be associated with worse outcomes of medical treatment (Bellelli et al., 2008; Lenze et al., 2007; Smith et al., 2015).

To manage mild to moderate depression in people with dementia, nonpharmacological interventions such as psychotherapy, reminiscence therapy, and personalized pleasant activities are recommended as first-line treatment (Kales et al., 2015; Orgeta et al., 2015; Testad et al., 2014). In severe depression, pharmacological treatment with antide-

\* Corresponding author.

E-mail address: [Ane.Erdal@uib.no](mailto:Ane.Erdal@uib.no) (A. Erdal).

pressants is recommended, although updated systematic reviews of the use of antidepressants for depression in people with dementia did not find conclusive evidence for efficacy in this population (Leong, 2014; Nelson and Devanand, 2011).

Thus far, little attention has been paid to potential modifiable causal factors of depression such as untreated chronic pain. Approximately 40–60% of nursing home patients are suggested to be in daily moderate to severe pain (Achterberg et al., 2010; Husebo et al., 2011). People with dementia are at particular risk of untreated pain because their ability to understand, evaluate, and verbally communicate symptom severity gradually decreases (Flo et al., 2014). This may trigger symptoms such as depression, agitation, and sleep problems (Ballard et al., 2009). The interrelationship between pain and depression, known as the “pain-depression dyad”, is well documented in people without dementia (Bair et al., 2003; Goldenberg, 2010). Although no clear aetiology has been established, the conditions are known to commonly coexist, mutually exacerbate each other, share common signal pathways and neurotransmitters, and respond to similar treatments (Chopra and Arora, 2014).

The pain-depression dyad is not sufficiently investigated in people with dementia (Bair et al., 2003; Goldenberg, 2010). Thus far, four cross-sectional studies have found a significant association between pain and depression in nursing home patients with moderate to severe dementia (Cipher and Clifford, 2004; Leong and Nuo, 2007; Malara et al., 2016; Williams et al., 2005), including one study which also reported the prevalence of pain and depression stratified by cognitive status (Leong and Nuo, 2007). The most recent study by Malara et al. (2016) included 233 patients at different stages of dementia and found a significant association between pain and depression as evaluated by a physician. Although these studies provide important insights, some had a low sample size, did not assess pain and/or depression with validated proxy-rated instruments, and all studies lack prospective data to evaluate whether pain is associated with future worsening of depression. In the current study, we investigate the prospective associations between pain and depression in nursing home patients with advanced dementia to explore whether pain may be an exacerbating factor for depression, or vice versa. We addressed the following research questions: i) Is the intensity of pain associated with the severity of depression? ii) Is change in pain over time associated with change in depression? iii) How are these associations affected by cognitive function and use of analgesic or antidepressant drugs?

## 2. Methods

### 2.1. Sample

We analysed prospective data from two independent multicentre studies in 6 counties of Norway. The REDIC (REsource Use and Disease Course in Dementia) study included all patients aged  $\geq 65$  years (or younger, if established dementia diagnosis) at admission to nursing home care with an expected stay of  $> 4$  weeks, and life expectancy  $> 6$  weeks, from January 2012 to June 2014 (Sandvik et al., 2016a). In total, 696 patients were included from 47 nursing homes. The current analyses use data collected at month 0 and 6, excluding 12 patients aged  $< 65$  years (Fig. 1). The other study, COSMOS (CCommunication, Systematic pain treatment, Medication review, Organized activities and Safety), included all patients aged  $\geq 65$  years in long-term nursing home care, excluding patients with diagnosis of schizophrenia or life expectancy  $< 6$  months, from April 2014 to June 2015 (Husebo et al., 2015). In total, 545 patients were included from 67 units (clusters) in 31 nursing homes. Clusters were randomised to receive either a complex intervention or care as usual (Husebo et al., 2015). The current analyses use data from the control group, comprising 247 patients from 26 units, collected at month 0 and 4 (Fig. 1).

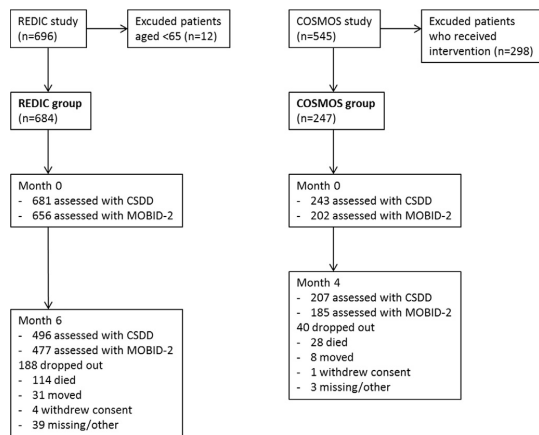


Fig. 1. Patients included in the final analyses.

### 2.2. Data collection

Data collection in both studies was completed in close collaboration with a staff member who had been familiar with the patients for a minimum of 4 weeks prior to data collection. The staff received training in the appropriate use of each outcome measure (Table 1), and had assistance from the researchers as needed. Demographic information and scheduled drug prescriptions (excluding prescriptions given “as needed”) were extracted from the patients’ medical records. Analgesic use at baseline and follow-up was assessed by counting the number of prescriptions for drugs classified as systemic analgesics (Anatomical Therapeutic Chemical (ATC) code N02 or M01A) at each time point. Similarly, antidepressant use was assessed by counting the number of prescriptions for drugs classified as antidepressants (ATC code N06A) at baseline and follow-up. We did not assess the appropriateness of dose; i.e. a dose adjustment from baseline to follow-up was not registered.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE), with scores from 26 to 30 defined as no/questionable, 21–25 as mild, 11–20 as moderate and 0–10 as severe cognitive impairment (Folstein et al., 1975; Pernecky et al., 2006). Pain was assessed using the Mobilisation-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale, with moderate to severe pain defined as a score of  $\geq 3$  (Husebo et al., 2014). Depressive symptoms were assessed using the Cornell Scale for Depression in Dementia (CSDD), and depression defined as a score of  $\geq 8$  (Alexopoulos et al., 1988; Burns et al., 2004). The Neuropsychiatric Inventory – Nursing Home version (NPI-NH) was used to assess neuropsychiatric symptoms (Cummings et al., 1994; Selbaek et al., 2008), and the NPI-depression subscale was used as a secondary outcome measure.

### 2.3. Statistical analysis

Baseline characteristics were described with mean and standard deviation (SD) for continuous variables and with number of patients and percentages of sample size for categorical variables. Differences at baseline between the studies were tested with independent samples *t*-tests for normally distributed continuous variables, Mann-Whitney *U*-test for non-normal distributed continuous variables and Pearson  $\chi^2$  tests for categorical variables. The unadjusted odds ratio (OR) for depression among patients with moderate to severe pain was calculated at baseline. Linear regression models were fitted to analyse the prospective association between pain at baseline and depression at follow-up, and vice versa, adjusted for depression, pain, age, sex, and cognitive function at baseline. To account for intra-cluster correlation



**Table 1**  
Assessment scales.

	What does the tool measure?	Tool characteristics and psychometric properties
MMSE	Staging of cognitive impairment based on scores in 8 domains (orientation to time and place, short-term recall, attention, calculation, long-term recall, language, repetition, and complex commands), questionnaire administered directly to the patient	30 items yield a sum score from severe (0–10), moderate (11–20), mild (21–25), to no cognitive impairment (26–30) (Folstein et al., 1975). Widely used as a screening tool, with good reliability and validity (Tombaugh and McIntyre, 1992).
MOBID-2 Pain Scale	Assessment of pain intensity in dementia inferred by observation of pain behaviours during standardised, guided movement (part 1 - musculoskeletal system; current) and previous observations of other pain behaviours (part 2 - internal organs, head and skin; in the last days), proxy rated	Each item is rated on a horizontal scale from 0 (no pain) to 10 (worst pain imaginable). Yields a final assessment of total pain (range 0–10) (Husebo et al., 2007). Excellent reliability and validity, good responsiveness (Husebo et al., 2014). Total pain $\geq 3$ was defined as moderate to severe pain.
CSDD	Depressive symptoms in people with dementia in 5 domains (mood-related signs, behavioural disturbance, physical signs, cyclic functions, and ideational disturbance) in the last week, proxy rated	19 items with each symptom score rated from 0 (not present) to 2 (severe) (Alexopoulos et al., 1988). Satisfactory interrater reliability and validity in the elderly population (Korner et al., 2006). Sum score $\geq 8$ defined as depression (Burns et al., 2004).
NPI-NH	The frequency and severity of 12 neuropsychiatric items in dementia (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, loss of inhibition, irritability/lability, aberrant motor behaviours, sleep and appetite and eating disturbances), proxy rated	The product of frequency (0–4) and severity (1–3) yields a composite score per item from 0 (not present) to 12 (most frequent and severe symptoms), with a cut-off value of $\geq 4$ for clinically significant symptoms. Sum score 0–144 (Cummings et al., 1994). The Norwegian version has shown good reliability and validity (Selbaek et al., 2008).

at the nursing home level, we used robust estimators for variance. To explore whether increasing pain was associated with increasing depression, and vice versa, we used linear mixed effect models with restricted maximum likelihood estimation. We conducted several analyses for the outcome variables where we included fixed effects for MOBID-2, CSDD, time, antidepressant use, and analgesic use (time-varying covariates), and MMSE, age, and sex (time-constant variables). Associations at different stages of cognitive functioning were assessed by stratifying according to MMSE (Perneczky et al., 2006). To account for intra-cluster correlation, the models were fitted with random intercept for both nursing home and patient-level effects. We included random slope for MOBID-2 and CSDD at patient-level, thus allowing the effects of these covariates to vary between patients. The covariance structures were specified using an independent model for both patients and nursing homes. The regression coefficients for the time-varying covariates can be interpreted as a between-patients effect and/or a within-patient effect. To investigate this further, we included both within and between effects in the same model (Rabe-Hesketh and Skrondal, 2012). Mixed model analyses were also conducted using NPI-depression as a dependent variable, with MOBID-2, time, MMSE, age, and sex as independent variables, to explore whether any associations obtained using the CSDD scale were replicated. We regarded  $p < .05$  as statistically significant. All analyses were conducted with Stata/IC version 14 (StataCorp LP, College Station, TX, USA).

#### 2.4. Ethical and legal considerations

Verbal and written informed consent was obtained from the patients if they had sufficient ability to consent; if not, written presumed consent was obtained from a legally authorised representative, in accordance with the ethics committee requirements and current Norwegian legislation. The REDIC and COSMOS trials were approved by the Regional Committees for Medical and Health Research Ethics, 2011/1738 and 2013/1765, and registered at [clinicaltrials.gov](http://clinicaltrials.gov), NCT01920100 and NCT02238652, respectively.

### 3. Results

We included 931 patients with a mean age of 85.4 (SD 7.0) and mean MMSE score of 14.6 (SD 7.1); 622 (66.8%) were women (Table 2). In total, 703 completed the follow-up assessments, 142 died, 39 moved home or to a different institution/ward, 5 withdrew consent to participate, and 42 were lost to follow-up for other reasons (Fig. 1). Compared to the REDIC study, participants included in the COSMOS trial were older and had a higher ratio of women. They had lower MMSE scores, more pain and depressive symptoms, neuropsychiatric

symptoms, and used more analgesics and antidepressants. At baseline, 343 of all patients (40.0% of those who completed the assessment) had moderate to severe pain (MOBID-2  $\geq 3$ ), 347 (37.6%) had depression (CSDD  $\geq 8$ ), and 164 (19.2% of 856 patients who completed both assessments) had both pain and depression. The unadjusted OR of patients with moderate to severe pain having depression was 2.35 (95% CI 1.76–3.12). MOBID-2 assessments at baseline and follow-up were completed by 617 patients, of whom 137 (22.2%) had moderate to severe pain at both assessments. Mean pain score was unchanged from baseline to follow-up, and 92 patients (14.9%) had new incidence moderate to severe pain at follow-up. CSDD assessments at baseline and follow-up were completed for 699 patients, of whom 144 (20.6%) had depression at both assessments, and 81 patients (11.6%) had new incidence depression at follow-up.

Using linear regression, we found that pain at baseline was significantly associated with depression at follow-up in both the REDIC and COSMOS groups (coefficients .26 and .70,  $p = .022$  and  $< .001$ , respectively). When adjusting for covariates, this association remained significant only in the COSMOS group (Table 3). Similarly, depression at baseline was significantly associated with pain at follow-up in both groups in the unadjusted analyses (coefficients .06 and .11 for REDIC and COSMOS, respectively,  $p < .001$ ), but only significantly in the REDIC group (coefficient .05,  $p = .008$ ) after adjusting for covariates.

Using linear mixed model analyses, adjusted for time (months), MMSE, age, and sex, we found that patients with more pain were significantly more depressed than those with less pain, and vice versa (Model 2, Table 4). An increase of 1 on the MOBID-2 scale was associated with an increase of .48 on the CSDD scale ( $p < .001$ ) and with an increase of .11 on the NPI-depression subscale ( $p = .005$ ). An increase of 1 on the CSDD scale was associated with an increase of .10 on the MOBID-2 scale ( $p < .001$ ). When measures of between- and within-subject effects were included in the model, only the between-subject effects were significant ( $p < .001$  for between-, and  $p = .113$  for within-subject effects). Over time, depression scores decreased in severity (.10 decrease in CSDD scores per month,  $p = .007$ ), as opposed to pain which remained unchanged. The severity of pain and depression was gender independent (coefficients .26,  $p = .069$ ;  $-.08$ ,  $p = .814$ ; respectively). Older patients had more pain (coefficient .02,  $p = .014$ ) but less depression ( $-.10$ ,  $p < .001$ ), and those with more severe cognitive impairment had more depression (1 point less on the MMSE scale was associated with .12 increase in CSDD,  $p < .001$ ), but not more pain (coefficient .00,  $p = .721$ ). However, the progression of depression over time (Fig. 2) was not affected by MMSE score ( $p = .990$ ). The mixed model analyses were re-calculated separately for the REDIC and COSMOS groups with unchanged results, except that the COSMOS

**Table 2**  
Characteristics of included patients at baseline; total and between groups.

	Total (n = 931)	N <sup>a</sup>	REDIC (n = 684)	N <sup>a</sup>	COSMOS (n = 247)	N <sup>a</sup>	p
Age <sup>b</sup>	85.4 (7.0)		84.8 (6.8)		87.0 (7.2)		< .001
Female <sup>b</sup>	622 (66.8%)	931	437 (63.9%)	684	185 (74.9%)	247	.002
MMSE <sup>a</sup>	14.6 (7.1)		15.7 (6.4)		11.4 (7.9)		< .001
MMSE ≤ 20 <sup>b</sup>	673 (80.2%)	839	487 (78.2%)	623	186 (86.1%)	216	.012
MOBID-2 <sup>c</sup>	2.3 (2.3)		2.1 (2.1)		2.8 (2.8)		.008
MOBID-2 ≥ 3 <sup>b</sup>	343 (40.0%)	858	249 (38.0%)	656	94 (46.5%)	202	.030
CSDD <sup>c</sup>	6.8 (5.6)		6.5 (5.2)		7.8 (6.4)		.017
CSDD ≥ 8 <sup>b</sup>	347 (37.6%)	924	243 (35.7%)	681	104 (42.8%)	243	.049
NPI-NH total score <sup>c</sup>	14.0 (17.0)	924	12.8 (15.3)	681	17.6 (20.7)	243	.012
NPI-NH depression <sup>c</sup>	1.8 (3.1)	909	1.9 (3.1)	675	1.7 (3.1)	234	.448
Analgesics <sup>d</sup>	445 (47.8%)		288 (42.1%)		157 (63.6%)		< .001
Antidepressants <sup>b</sup>	292 (31.4%)		193 (28.2%)		99 (40.1%)		.001

Numbers represent mean (SD) or number of patients (%).  
MMSE: Mini-Mental State Examination; NPI-NH: Neuropsychiatric Inventory-Nursing Home Version.  
<sup>a</sup> Number of patients who completed each assessment.  
<sup>b</sup> Independent-samples *t*-test.  
<sup>c</sup> Pearson  $\chi^2$ -test.  
<sup>d</sup> Mann-Whitney *U*-test.

**Table 3**  
Linear regression; associations with pain and depression at follow-up.

Dependent variable (follow-up)	Independent variable (baseline)	REDIC (n = 453)		COSMOS (n = 158)	
		Coef.	p	Coef.	p
CSDD	MOBID-2 (unadjusted)	.26	.022 <sup>*</sup>	.70	< .001 <sup>†</sup>
	CSDD	.08	.358	.41	.026 <sup>*</sup>
MOBID-2	CSDD	.48	< .001 <sup>†</sup>	.49	< .001 <sup>†</sup>
	MMSE	-.04	.357	-.07	.188
	Sex	.30	.347	.32	.802
	Age	-.08	.007 <sup>*</sup>	.01	.818
MOBID-2					
MOBID-2					
	CSDD (unadjusted)	.06	< .001 <sup>†</sup>	.11	< .001 <sup>†</sup>
	CSDD	.05	.008 <sup>*</sup>	.06	.064
	MOBID-2	.38	< .001 <sup>†</sup>	.38	.005
	MMSE	.03	.039	-.01	.849
	Sex	.13	.531	.37	.435
Age	.01	.395	-.01	.800	

COSMOS, *CO*munication, *S*ystematic pain treatment, *M*edication review, *O*rganized activities and *S*afety Study; CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale; REDIC, *RE*source Use and *D*isease Course in *D*ementia Study. Analyses include all patients with valid assessments at baseline and follow-up, and are adjusted for intra-cluster effects at the nursing home level.  
<sup>\*</sup> Significant association at  $p < .05$  level.

population did not have a significant reduction in depressive symptoms over time (coefficient  $-.08$ ,  $p = .474$ ). The REDIC population had a significant within-subject effect of pain on depressive symptoms, i.e. a patient who had reduced pain at follow-up had significantly less depressive symptoms at follow-up compared to baseline (between-subject coefficient  $.62$ ,  $p < .001$ , within-subject coefficient  $.23$ ,  $p = .042$ ). In the COSMOS population, only the between-subject effects were significant ( $p = .317$  for individual effects).

The associations between pain and depressive symptoms remained significant when use of analgesics and/or antidepressants at baseline and follow-up was included in the mixed models (Model 3–5, Table 4). Use of analgesics was significantly associated with pain and depression. A patient who received an increased number of analgesics from baseline to follow-up had significantly increased pain (coefficient  $.65$ ,  $p < .001$ ) and increased depression ( $.49$ ,  $p = .006$ ) in the same period (Model 4, Table 4). Number of prescribed antidepressants was significantly

associated with depressive symptoms ( $1.2$ ,  $p < .001$ ), but not with pain ( $-.02$ ,  $p = .873$ ) (Model 3, Table 4).

When patients were grouped according to cognitive function, pain was significantly associated with increased depression in people with mild (coefficient  $.47$ ,  $p = .005$ ) and moderate ( $.62$ ,  $p < .001$ ) cognitive impairment, and near-significantly in those with severe cognitive impairment ( $.24$ ,  $p = .050$ ; Table 5), but not significantly associated in those with no/questionable impairment ( $.39$ ,  $p = .232$ ). Correspondingly, depression was associated with pain in mild ( $.09$ ,  $p = .008$ ), moderate ( $.12$ ,  $p < .001$ ), and severe ( $.06$ ,  $p = .016$ ) cognitive impairment, but not in those with no/questionable impairment ( $.07$ ,  $p = .229$ ).

## 4. Discussion

### 4.1. Discussion

This study confirms the continued existence of the pain-depression dyad in nursing home patients irrespective of cognitive status. Moreover, this study is the first to show that reduced pain intensity is associated with future reduction of depressive symptoms in this population. This is the first large-scale multicentre prospective study investigating the associations between pain and depression over time in nursing home patients at all stages of cognitive impairment, using validated proxy-rated instruments with good validity, reliability, and responsiveness, and controlling for intra-cluster correlation and use of analgesics and/or antidepressants. The obtained OR of depression in patients with moderate to severe pain (unadjusted OR 2.35, 95% CI 1.76–3.12) was similar to results from previous nursing home studies (Cipher and Clifford, 2004; Gruber-Baldini et al., 2005; Leong and Nuo, 2007; Malara et al., 2016; Williams et al., 2005).

Although we found that the association between pain and depressive symptoms was strongest in patients with moderate cognitive impairment (Table 5), the difference in effect between the four stages of cognitive impairment was not significant ( $p = .227$ ). This means that we did not find evidence to suggest that the association changed with increasing severity of cognitive impairment. In patients with no/questionable impairment, the association was nonsignificant, probably because this group was smaller ( $n = 49$ ). Patients with severe cognitive impairment appear to have a weaker association than those with moderate impairment, which did not reach significance despite this group being relatively large ( $n = 201$ ), but the difference in effect was not significant with the current sample size.

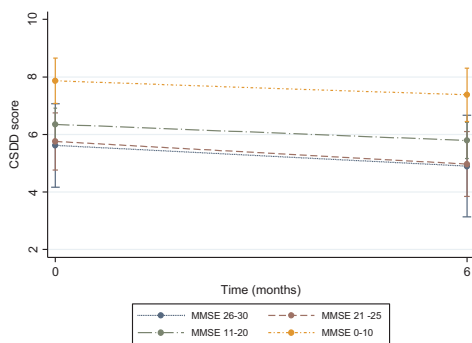
At baseline, 48% received one or more analgesics, while 40% still had moderate to severe pain. A previous study found that in 2011, 58%

**Table 4**  
Results from mixed model analyses; unstratified.

Dependent variable	Independent variable	Model 1		Model 2		Model 3		Model 4		Model 5	
		C	p	C	p	C	p	C	p	C	p
CSDD	MOBID-2	.45	< .001 <sup>†</sup>	.48	< .001 <sup>†</sup>	.48	< .001 <sup>†</sup>	.44	< .001 <sup>†</sup>	.44	< .001 <sup>†</sup>
	Time (months)	-.11	.002	-.10	.007 <sup>†</sup>	-.11	.002 <sup>†</sup>	-.11	.003 <sup>†</sup>	-.12	.001 <sup>†</sup>
	MMSE			-.12	< .001 <sup>†</sup>	-.12	< .001 <sup>†</sup>	-.12	< .001 <sup>†</sup>	-.12	< .001 <sup>†</sup>
	Age			-.10	< .001 <sup>†</sup>	-.09	< .001 <sup>†</sup>	-.11	< .001 <sup>†</sup>	-.09	< .001 <sup>†</sup>
	Sex			-.08	.814	-.30	.381	-.13	.711	-.32	.336
	Antidepressants					1.2	< .001 <sup>†</sup>			1.2	< .001 <sup>†</sup>
MOBID-2	Analgesics							.49	.006 <sup>†</sup>	.41	.023 <sup>†</sup>
	CSDD	.09	< .001 <sup>†</sup>	.10	< .001 <sup>†</sup>	.10	< .001 <sup>†</sup>	.09	< .001 <sup>†</sup>	.09	< .001 <sup>†</sup>
	Time (months)	.01	.560	.01	.398	.01	.393	.00	.927	.00	.973
	MMSE			.00	.721	.00	.715	.00	.795	.00	.768
	Age			.02	.014 <sup>†</sup>	.02	.015 <sup>†</sup>	.02	.052	.02	.065
	Sex			.26	.069	.26	.068	.18	.180	.19	.153
	Antidepressants					-.02	.873			-.08	.440
	Analgesics							.65	< .001 <sup>†</sup>	.65	< .001 <sup>†</sup>

**Model 1:** Association between pain and depression over time, unadjusted; **Model 2:** Association between pain and depression over time, adjusted for cognitive function, age, and sex; **Model 3:** Association between pain and depression over time, adjusted for number of prescribed antidepressants, cognitive function, age, and sex; **Model 4:** Association between pain and depression over time, adjusted for number of prescribed analgesics, cognitive function, age, and sex; **Model 5:** Association between pain and depression over time, adjusted for number of prescribed antidepressants and analgesics, cognitive function, age, and sex. C, coefficient; CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale. Analyses include all patients with valid assessments at any time point, and are adjusted for time to follow-up (4/6 months) and intra-cluster effects at the nursing home level.

<sup>†</sup> Significant association at p < .05 level.



**Fig. 2.** Mixed model; course of depressive symptoms by cognitive function.

of nursing home residents in Norway were prescribed analgesics (Sandvik et al., 2016b). While we found a lower overall prescription rate, this is probably explained by the large proportion of recently admitted nursing home patients in our sample. In the COSMOS group, which is more comparable to the general nursing home population,

64% received analgesics. This may indicate a slight increase in analgesic use from 2011 to 2014. A higher number of prescribed analgesics at baseline, or an increase in the number of prescribed analgesics from baseline to follow-up, was associated with higher levels of both pain and depression. One explanation for this may be that the prescribed treatment was insufficient to relieve pain effectively. Another possibility is that use of one or more analgesics may increase the total symptom burden due to adverse effects or interactions between analgesics or other psychotropic drugs such as sedatives. Known adverse effects of opioid analgesics in the elderly, such as sedation or reduced appetite (Chau et al., 2008), may also have been reported as symptoms of depression.

At baseline, 38% had depression and 31% received antidepressants. A recent systematic review found that in Western nursing homes from 2004 to present, the use of antidepressants ranged from 18% to 48%, and in the Nordic countries from 39% to 43% (Janus et al., 2016). In the COSMOS sample, 40% used antidepressants, which is consistent with these previous reports. Systematic reviews and meta-analyses have not found clear benefit of antidepressants for moderate to severe depression in people with dementia (Leong, 2014; Nelson and Devanand, 2011), despite this the rate of antidepressant use in nursing home patients appears to remain unchanged (Gulla et al., 2016; Janus et al., 2016). We found that antidepressant use was associated with

**Table 5**  
Mixed model, stratified for level of cognitive impairment.

Dependent variable	Independent variable	MMSE 0–10 (N = 201)		MMSE 11–20 (N = 453)		MMSE 21–25 (N = 115)		MMSE 26–30 (N = 49)		P-value <sup>a</sup>
		Coefficient	p	Coefficient	p	Coefficient	p	Coefficient	p	
CSDD	MOBID-2	.24	.050	.62	< .001 <sup>†</sup>	.47	.005 <sup>†</sup>	.39	.232	.227
	Time (months)	-.08	.322	-.10	.042 <sup>†</sup>	-.13	.156	-.10	.436	.978
	Sex	.72	.392	-.45	.290	-.03	.967	.65	.706	.700
	Age	-.09	.086	-.09	.006 <sup>†</sup>	-.13	.019	-.11	.284	.830
MOBID-2	CSDD	.06	.016 <sup>†</sup>	.12	< .001 <sup>†</sup>	.09	.008 <sup>†</sup>	.07	.229	.381
	Time (months)	-.06	.161	.04	.033 <sup>†</sup>	.02	.626	.00	.985	.165
	Sex	.49	.126	.09	.612	-.12	.751	1.5	.018 <sup>†</sup>	.024 <sup>†</sup>
	Age	.04	.076	.02	.096	.00	.871	.01	.762	.417

CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale. Analyses include all patients with valid assessments at any time point, adjusted for time to follow-up (4/6 months) and intra-cluster effects at the nursing home level.

<sup>†</sup> Significant association at p < .05 level.

<sup>a</sup> P for interaction is a test for difference in effect between the separate groups.

higher levels of depression. Similar results have been reported previously, possibly due to inconclusive efficacy combined with increased likelihood of prescribing to those with severe depressive symptoms (Borza et al., 2015). While the efficacy of antidepressants for depression in people with dementia is uncertain and may be difficult to assess, elderly patients with dementia are also particularly susceptible to adverse effects and drug interactions (Gulla et al., 2016). Increased risks of seizures, falls, fractures, and mortality have been reported in older patients receiving antidepressants (Bakken et al., 2013; Coupland et al., 2011).

The therapeutic benefit of analgesic and antidepressant drugs should be assessed regularly with validated tools, and weighed carefully against potential adverse effects. Future advances should go towards systematic symptom assessment in people with dementia, in order to identify those in need of treatment, and to stop unnecessary or harmful treatment.

#### 4.2. Limitations

This study has its limitations. Due to the observational design of the study, we cannot draw conclusions on causality from this material. Furthermore, the REDIC and COSMOS trials had different inclusion criteria. The REDIC trial, which contributed the majority of our population, included patients at admission to nursing home care. Thus our results may not be directly generalisable to other populations with varying lengths of stay. Nursing home admission is associated with increase of depressive symptoms, which may not be congruent with depressive disorder (Achterberg et al., 2006). However, the persistence rate of depression 6 months after admission has been estimated to 63% (Smalbrugge et al., 2006), which is similar to that found in other studies (Selbaek et al., 2013), and to our observed rate (67%). The proportion of recently admitted patients could also strengthen our results, as the length of stay in nursing home care is typically short. A UK study found that 53% died within 6 months of admission, while a small number of patients stayed much longer, increasing the average stay to 14 months (Kelly et al., 2010). Though time to follow-up differed between the REDIC and COSMOS trials, the mixed model analyses included a time variable to ensure that this did not affect the results. The main analyses (Table 4) were re-calculated separately for each group, with unchanged results. The combined data set enabled us to include a high number of patients, recruited from a wide network of research centres, controlling for possible confounding factors to ensure robustness of results. Some potential sources of confounding remain. The number of scheduled prescriptions for any analgesic or antidepressant was recorded at each time point, but we did not assess the duration of use, appropriateness of the prescribed dose, or changes in the prescribed doses of individual drugs. Nor did we assess any use of as-needed drugs. Furthermore, use of nonpharmacological interventions for either pain or depression was not assessed. While the CSDD scale includes some items that may overlap with pain, such as “multiple physical complaints”, pain was significantly associated with NPI depression, reducing the likelihood that our results are due to symptom overlap.

#### 5. Conclusion

We found highly significant, prospective associations between pain and depression, irrespective of analgesic or antidepressant use. These associations were replicated in groups with mild, moderate, and severe cognitive impairment. Because a reduction in pain was associated with less depressive symptoms, patients with dementia should be regularly assessed for untreated pain. The benefit of analgesic or antidepressant drugs should also be assessed regularly and weighed carefully against the potential for adverse effects.

#### References

- Achterberg, W., Pot, A.M., Kerkstra, A., Ribbe, M., 2006. Depressive symptoms in newly admitted nursing home residents. *Int. J. Geriatr. Psychiatry* 21, 1156–1162.
- Achterberg, W.P., Gambassi, G., Finne-Soveri, H., Liperoti, R., Noro, A., Frijters, D.H., Cherubini, A., Dell’Aquila, G., Ribbe, M.W., 2010. Pain in European long-term care facilities: cross-national study in Finland, Italy and The Netherlands. *Pain* 148, 70–74.
- Alexopoulos, G.S., Abrams, R.C., Young, R.C., Shamoian, C.A., 1988. Cornell Scale for Depression in Dementia. *Biol. Psychiatry* 23, 271–284.
- Bair, M.J., Robinson, R.L., Katon, W., Kroenke, K., 2003. Depression and pain comorbidity: a literature review. *Arch. Intern. Med.* 163, 2433–2445.
- Bakken, M.S., Engeland, A., Engesaeter, L.B., Ranhoff, A.H., Hunskar, S., Ruths, S., 2013. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. *Age Ageing* 42, 514–520.
- Ballard, C., Corbett, A., Chitramohan, R., Aarsland, D., 2009. Management of agitation and aggression associated with Alzheimer’s disease: controversies and possible solutions. *Curr. Opin. Psychiatry* 22, 532–540.
- Bellelli, G., Frisoni, G.B., Turco, R., Trabucchi, M., 2008. Depressive symptoms combined with dementia affect 12-months survival in elderly patients after rehabilitation post-hip fracture surgery. *Int. J. Geriatr. Psychiatry* 23, 1073–1077.
- Borza, T., Engedal, K., Bergh, S., Barca, M.L., Benth, J.S., Selbaek, G., 2015. The course of depressive symptoms as measured by the Cornell scale for depression in dementia over 74 months in 1158 nursing home residents. *J. Affect. Disord.* 175, 209–216.
- Burns, A., Lawlor, B., Craig, S., 2004. Assessment Scales in Old Age Psychiatry. CRC Press, London.
- Chau, D.L., Walker, V., Pai, L., Cho, L.M., 2008. Opiates and elderly: use and side effects. *Clin. Interv. Aging* 3, 273–278.
- Chopra, K., Arora, V., 2014. An intricate relationship between pain and depression: clinical correlates, coactivation factors and therapeutic targets. *Expert Opin. Ther. Targets* 18, 159–176.
- Cipher, D.J., Clifford, P.A., 2004. Dementia, pain, depression, behavioral disturbances, and ADLs: toward a comprehensive conceptualization of quality of life in long-term care. *Int. J. Geriatr. Psychiatry* 19, 741–748.
- Coupland, C., Dhiman, P., Morris, R., Arthur, A., Barton, G., Hippisley-Cox, J., 2011. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *Br. Med. J.* 343, d4551.
- Cummings, J.L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D.A., Gornbein, J., 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44, 2308–2314.
- Enache, D., Winblad, B., Aarsland, D., 2011. Depression in dementia: epidemiology, mechanisms, and treatment. *Curr. Opin. Psychiatry* 24, 461–472.
- Flo, E., Gulla, C., Husebo, B.S., 2014. Effective pain management in patients with dementia: benefits beyond pain? *Drugs Aging* 31, 863–871.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198.
- Goldenberg, D.L., 2010. Pain/Depression dyad: a key to a better understanding and treatment of functional somatic syndromes. *Am. J. Med.* 123, 675–682.
- Gonzalez-Salvador, T., Lyketsos, C.G., Baker, A., Hovanec, L., Roques, C., Brandt, J., Steele, C., 2000. Quality of life in dementia patients in long-term care. *Int. J. Geriatr. Psychiatry* 15, 181–189.
- Gruber-Baldini, A.L., Zimmerman, S., Boustani, M., Watson, L.C., Williams, C.S., Reed, P.S., 2005. Characteristics associated with depression in long-term care residents with dementia. *Gerontologist* 45 (Special Issue 1), 50–55.
- Gulla, C., Selbaek, G., Flo, E., Kjøme, R., Kirkevold, O., Husebo, B.S., 2016. Multi-psychotropic drug prescription and the association to neuropsychiatric symptoms in three Norwegian nursing home cohorts between 2004 and 2011. *BMC Geriatr.* 16, 115.
- Helvik, A.S., Engedal, K., Benth, J.S., Selbaek, G., 2015. Prevalence and severity of dementia in nursing home residents. *Dement. Geriatr. Cogn. Disord.* 40, 166–177.
- Husebo, B.S., Ballard, C., Sandvik, R., Nilsen, O.B., Aarsland, D., 2011. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *Br. Med. J.* 343, d4065.
- Husebo, B.S., Flo, E., Aarsland, D., Selbaek, G., Testad, I., Gulla, C., Aasmul, I., Ballard, C., 2015. COSMOS – improving the quality of life in nursing home patients: protocol for an effectiveness-implementation cluster randomized clinical hybrid trial. *Implement. Sci.* 10, 131.
- Husebo, B.S., Ostelo, R., Strand, L.L., 2014. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. *Eur. J. Pain.* 18, 1419–1430.
- Husebo, B.S., Strand, L.L., Moe-Nilssen, R., Husebo, S.B., Snow, A.L., Ljunggren, A.E., 2007. Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID): development and validation of a nurse-administered pain assessment tool for use in dementia. *J. Pain. Symptom Manag.* 34, 74–80.
- Janus, S.I., van Manen, J.G., Ijzerman, M.J., Zuidema, S.U., 2016. Psychotropic drug prescriptions in Western European nursing homes. *Int. Psychogeriatr.* 28, 1–16.
- Janzing, J.G., Bouwens, J.M., Teunisse, R.J., Van’t Hof, M.A., Zitman, F.G., 1999. The relationship between depression and mortality in elderly subjects with less severe dementia. *Psychol. Med.* 29, 979–983.
- Kales, H.C., Gitlin, L.N., Lyketsos, C.G., 2015. Assessment and management of behavioral and psychological symptoms of dementia. *Br. Med. J.* 350, h369.
- Kelly, A., Conell-Price, J., Covinsky, K., Cenzer, I.S., Chang, A., Boscardin, W.J., Smith, A.K., 2010. Length of stay for older adults residing in nursing homes at the end of life. *J. Am. Geriatr. Soc.* 58, 1701–1706.

- Korner, A., Lauritzen, L., Abelskov, K., Gulmann, N., Marie Brodersen, A., Wedervang-Jensen, T., Marie Kjeldgaard, K., 2006. The Geriatric Depression Scale and the Cornell Scale for Depression in Dementia. A validity study. *Nord. J. Psychiatry* 60, 360–364.
- Lenze, E.J., Skidmore, E.R., Dew, M.A., Butters, M.A., Rogers, J.C., Begley, A., Reynolds 3rd, C.F., Munin, M.C., 2007. Does depression, apathy or cognitive impairment reduce the benefit of inpatient rehabilitation facilities for elderly hip fracture patients? *Gen. Hosp. Psychiatry* 29, 141–146.
- Leong, C., 2014. Antidepressants for depression in patients with dementia: a review of the literature. *Consult. Pharm.* 29, 254–263.
- Leong, I.Y., Nuo, T.H., 2007. Prevalence of pain in nursing home residents with different cognitive and communicative abilities. *Clin. J. Pain* 23, 119–127.
- Luppa, M., Luck, T., Brahler, E., König, H.H., Riedel-Heller, S.G., 2008. Prediction of institutionalisation in dementia. A systematic review. *Dement. Geriatr. Cogn. Disord.* 26, 65–78.
- Malara, A., De Biase, G.A., Bettarini, F., Ceravolo, F., Di Cello, S., Garo, M., Praino, F., Settembrini, V., Sgrò, G., Spadea, F., Rispoli, V., 2016. Pain assessment in elderly with behavioral and psychological symptoms of dementia. *J. Alzheimers Dis.* 50, 1217–1225.
- Nelson, J.C., Devanand, D.P., 2011. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J. Am. Geriatr. Soc.* 59, 577–585.
- Orgeta, V., Qazi, A., Spector, A., Orrell, M., 2015. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *Br. J. Psychiatry* 207, 293–298.
- Perneczky, R., Wagenpfeil, S., Komossa, K., Grimmer, T., Diehl, J., Kurz, A., 2006. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am. J. Geriatr. Psychiatry* 14, 139–144.
- Potter, G.G., Steffens, D.C., 2007. Contribution of depression to cognitive impairment and dementia in older adults. *Neurologist* 13, 105–117.
- Rabe-Hesketh, S., Skrondal, A., 2012. *Multilevel and Longitudinal Modeling Using Stata*, 3rd ed. Stata Press, Texas, pp. 152–156.
- Rapp, M.A., Schnaider-Beeri, M., Wysocki, M., Guerrero-Berroa, E., Grossman, H.T., Heinz, A., Haroutunian, V., 2011. Cognitive decline in patients with dementia as a function of depression. *Am. J. Geriatr. Psychiatry* 19, 357–363.
- Sandvik, R.K., Selbaek, G., Bergh, S., Aarsland, D., Husebo, B.S., 2016a. Signs of imminent dying and change in symptom intensity during pharmacological treatment in dying nursing home patients: a prospective trajectory study. *J. Am. Med. Dir. Assoc.* 17, 821–827.
- Sandvik, R.K., Selbaek, G., Kirkevold, O., Husebo, B.S., Aarsland, D., 2016b. Analgesic prescribing patterns in Norwegian nursing homes from 2000 to 2011: trend analyses of four data samples. *Age Ageing* 45, 54–60.
- Selbaek, G., Engedal, K., 2012. Stability of the factor structure of the Neuropsychiatric Inventory in a 31-month follow-up study of a large sample of nursing-home patients with dementia. *Int. Psychogeriatr.* 24, 62–73.
- Selbaek, G., Engedal, K., Bergh, S., 2013. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. *J. Am. Med. Dir. Assoc.* 14, 161–169.
- Selbaek, G., Kirkevold, O., Sommer, O.H., Engedal, K., 2008. The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, nursing home version (NPI-NH). *Int. Psychogeriatr.* 20, 375–382.
- Smalbrugge, M., Jongenelis, L., Pot, A.M., Eefsting, J.A., Ribbe, M.W., Beekman, A.T., 2006. Incidence and outcome of depressive symptoms in nursing home patients in the Netherlands. *Am. J. Geriatr. Psychiatry* 14, 1069–1076.
- Smith, T.O., Hameed, Y.A., Cross, J.L., Henderson, C., Sahota, O., Fox, C., 2015. Enhanced rehabilitation and care models for adults with dementia following hip fracture surgery. *Cochrane Database Syst. Rev.* 6, 1–47, Article no. CD010569.
- Testad, I., Corbett, A., Aarsland, D., Lexow, K.O., Fossey, J., Woods, B., Ballard, C., 2014. The value of personalized psychosocial interventions to address behavioral and psychological symptoms in people with dementia living in care home settings: a systematic review. *Int. Psychogeriatr.* 26, 1083–1098.
- Todd, S., Barr, S., Roberts, M., Passmore, A.P., 2013. Survival in dementia and predictors of mortality: a review. *Int. J. Geriatr. Psychiatry* 28, 1109–1124.
- Tombaugh, T.N., McIntyre, N.J., 1992. The mini-mental state examination: a comprehensive review. *J. Am. Geriatr. Soc.* 40, 922–935.
- Williams, C.S., Zimmerman, S., Sloane, P.D., Reed, P.S., 2005. Characteristics associated with pain in long-term care residents with dementia. *Gerontologist* 45 (Special Issue 1), 68–73.

---

**Paper II**

**II**

# Efficacy and Safety of Analgesic Treatment for Depression in People with Advanced Dementia: Randomised, Multicentre, Double-Blind, Placebo-Controlled Trial (DEP.PAIN.DEM)

Ane Erdal<sup>1</sup>  · Elisabeth Flo<sup>2</sup> · Dag Aarsland<sup>3</sup> · Clive Ballard<sup>4</sup> · Dagrun D. Slettebo<sup>1</sup> · Bettina S. Husebo<sup>1,5</sup>

© The Author(s) 2018

## Abstract

**Background** Chronic pain and depression often co-occur, and pain may exacerbate depression in people with dementia.

**Objective** The objective of this study was to assess the efficacy and safety of analgesic treatment for depression in nursing home patients with advanced dementia and clinically significant depressive symptoms.

**Methods** We conducted a multicentre, parallel-group, double-blind, placebo-controlled trial in 47 nursing homes, including 162 nursing home patients aged  $\geq 60$  years with dementia (Mini-Mental State Examination  $\leq 20$ ) and depression (Cornell Scale for Depression in Dementia  $\geq 8$ ). Patients were randomised to receive active analgesic treatment (paracetamol or buprenorphine transdermal system) or identical placebo for 13 weeks. The main outcome measure was the change in depression (Cornell Scale

for Depression in Dementia) from baseline to 13 weeks, assessed using linear mixed models with fixed effects for time, intervention and their interaction in the models. Secondary outcomes were to assess whether any change in depression was secondary to change in pain (Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale) and adverse events.

**Results** The mean depression change was  $-0.66$  (95% confidence interval  $-2.27$  to  $0.94$ ) in the active group ( $n = 80$ ) and  $-3.30$  ( $-4.68$  to  $-1.92$ ) in the placebo group ( $n = 82$ ). The estimated treatment effect was  $2.64$  ( $0.55$ – $4.72$ ,  $p = 0.013$ ), indicating that analgesic treatment had no effect on depressive symptoms from baseline to 13 weeks while placebo appeared to ameliorate depressive symptoms. There was no significant reduction in pain in the active treatment group (paracetamol and buprenorphine combined) vs. placebo; however, a subgroup analysis demonstrated a significant reduction in pain for paracetamol vs. placebo [by  $-1.11$  ( $-2.16$  to  $-0.06$ ,  $p = 0.037$ )] from week 6 to 13 without a change in depression. Buprenorphine did not have significant effects on depression [ $3.04$  ( $-0.11$  to  $6.19$ ),  $p = 0.059$ ] or pain [ $0.47$  ( $-0.77$  to  $1.71$ ),  $p = 0.456$ ] from 0 to 13 weeks. Thirty-five patients were withdrawn from the study because of adverse reactions, deterioration or death: 25 (31.3%) during active treatment [23 (52.3%) who received buprenorphine], and ten (12.2%) in the placebo group. The most frequently occurring adverse events were psychiatric (17 adverse reactions) and neurological (14 adverse reactions).

**Conclusion** Analgesic treatment did not reduce depression while placebo appeared to improve depressive symptoms significantly by comparison, possibly owing to the adverse effects of active buprenorphine. The risk of adverse events

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s40266-018-0546-2>) contains supplementary material, which is available to authorized users.

✉ Ane Erdal  
ane.erdal@uib.no

<sup>1</sup> Department of Global Public Health and Primary Care, Centre for Elderly and Nursing Home Medicine, University of Bergen, Bergen, Norway

<sup>2</sup> Department of Clinical Psychology, University of Bergen, Bergen, Norway

<sup>3</sup> Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

<sup>4</sup> University of Exeter, Exeter, UK

<sup>5</sup> Department of Health and Care, Municipality of Bergen, Bergen, Norway

warrants caution when prescribing buprenorphine for people with advanced dementia.

*Trial registration* ClinicalTrials.gov NCT02267057 (registered 7 July, 2014) and Norwegian Medicines Agency EudraCT 2013-002226-23.

### Key Points

Contrary to our hypothesis, patients who received active analgesic treatment had more persistent depressive symptoms

The buprenorphine transdermal system may exacerbate neuropsychiatric symptoms in dementia and should be used with caution in this group

## 1 Introduction

Approximately 40% of nursing home patients receive antidepressants [1], and over 80% have dementia [2]. Although some studies suggest that antidepressants may be beneficial for depression in people with dementia [3, 4], several later studies have found negative results [5, 6]. The most commonly prescribed antidepressants are selective serotonin reuptake inhibitors such as sertraline, and norenergic and specific serotonergic antidepressants such as mirtazapine [7]. Lyketsos et al. found that sertraline reduced depression in Alzheimer's disease compared with placebo ( $n = 44$ ) [4], this result was followed by a larger study from the same group which found no benefit of sertraline compared with placebo ( $n = 131$ ) [6]. Banerjee et al. found that sertraline or mirtazapine did not reduce depression in dementia, and that participants who received active treatment had significantly higher rates of adverse events such as nausea and sedation compared with placebo ( $n = 326$ ) [5]. Updated systematic reviews and meta-analyses conclude that the current evidence base for antidepressants in dementia is equivocal [8, 9].

More than 60% of nursing home patients experience pain, often of moderate-to-severe intensity [10, 11]. Failure to systematically assess and treat pain leads to the risk of chronic pain, particularly in people with dementia who gradually lose their ability to reliably describe symptom severity [12]. Pain has been identified as a possible contributing factor to depression in nursing homes, even in patients with advanced dementia [13, 14]. Pain and depression share a complex relationship, known as the pain-depression dyad, implying that the conditions

commonly coexist, exacerbate each other, share common signal pathways and neurotransmitters, and respond to similar treatments [15]. A previous cluster randomised trial suggests that a 12-week stepwise protocol for treating pain with paracetamol, buprenorphine transdermal system (TDS), morphine or pregabalin may reduce depressive symptoms in people with advanced dementia and agitation [16]. However, depression was not an inclusion criterion in this study, and the pain intervention was not placebo controlled.

Buprenorphine is currently recommended for opioid analgesia in the elderly [17]. As a partial agonist/antagonist, it provides effective analgesia with a low potential for serious adverse effects including respiratory depression [17]. Because it undergoes hepatic metabolism and excretion, it does not require dose adjustment in renal insufficiency [17]. Some evidence suggests that buprenorphine may also have a potential for mood-elevating effects in depression [18]. Paracetamol is the most widely used non-opioid analgesic in the elderly, and may also exert an effect in the central processing and response to emotional stimuli [19].

Therefore, we wished to examine whether a stepwise protocol for treating pain using paracetamol or buprenorphine ameliorated depressive symptoms in nursing home patients with moderate-to-severe dementia and clinically significant depressive symptoms, controlling for the choice of analgesic, the presence of moderate-to-severe pain and dementia severity. To assess whether any change in depressive symptoms was secondary to an analgesic effect, we also examined whether the intervention effectively reduced pain compared with placebo.

## 2 Materials and Methods

### 2.1 Study Design

This was a 13-week, multicentre, parallel-group, double-blind, randomised placebo-controlled trial conducted in long-term and dementia wards in 47 nursing homes from 12 municipalities in Norway (Bergen, Baerum, Fjell, Kvam, Meland, Os, Oslo, Sandnes, Stavanger, Sula, Sund and Aalesund). Depending on ongoing medical treatment and clinical investigation, participants were prescribed either paracetamol tablets (maximum 3 g/day) or buprenorphine TDS (maximum 10 µg/hour), and were randomised to receive either active treatment or placebo.

### 2.2 Participants

We screened 2323 nursing home patients for inclusion from 18 August, 2014 to 13 September, 2016. Data



collection was completed by 20 December, 2016. Eligible participants were elderly ( $\geq 60$  years) long-term patients (i.e. residents with permanent placement) who had been living in the participating ward for at least 4 weeks prior to screening, with dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for major neurocognitive disorders, Mini-Mental State Examination (MMSE) score  $\leq 20$  [20] and clinically significant depression [Cornell Scale for Depression in Dementia (CSDD) score  $\geq 8$  at screening] of at least 4 weeks' duration [21]. Exclusion criteria were: cognitive impairment related to other diagnoses than Alzheimer's disease; frontotemporal dementia; vascular dementia; dementia with Lewy bodies or mixed dementia (e.g. traumatic head injury, chronic alcohol abuse or Huntington's disease; assessed by a review of medical records); life expectancy  $< 6$  months; severe pain [Mobilisation-Observation-Behaviour-Intensity-Dementia-2 (MOBID-2) Pain Scale score  $\geq 8$ ] [22]; severe aggression (with Neuropsychiatric Inventory—Nursing Home version aggression item  $\geq 8$ ) [23]; suicide risk; severe hepatic or renal insufficiency; anaemia (haemoglobin  $< 8.5$  mmol/L in men,  $< 7.5$  mmol/L in women); severe disease or injury that could interfere with study participation; comatose state; participation in another experimental trial; having no carer who was familiar with the patient; diagnosis of psychosis or other severe mental disorder prior to dementia diagnosis (e.g. schizophrenia, schizoaffective disorder and bipolar disorder); severe psychiatric or neurological disorder; uncontrolled epilepsy; the clinician responsible for care or study clinician considered that the patient had any physical condition that would make participation in the trial distressing or likely to increase patient discomfort; contraindication, known allergy, adverse reaction or clinically significant drug interaction to the assigned study treatment; and scheduled prescriptions for any opioid analgesic other than or exceeding buprenorphine  $5 \mu\text{g}/\text{hour}$ . When a patient at any point fulfilled any one exclusion criterion, we conducted no further assessments and the reason for exclusion was recorded.

At baseline, after a minimum of 4 weeks, we re-assessed the eligible patients for depression. To avoid false negatives at this point, we excluded patients who scored below the cut-off for greatest sensitivity on the CSDD scale (CSDD score  $\geq 6$ ). The screening cut-off value of  $\geq 8$  and the re-assessment threshold for persistent depression of  $\geq 6$  on the CSDD scale correspond to the optimal cut-off points for specificity and sensitivity, respectively, as summarised in a recent meta-analysis [24].

### 2.3 Randomisation and Masking

The trial was double blinded, and participants were randomly allocated to each arm in a 1:1 ratio according to computer-generated random numbers in blocks of ten (paracetamol) and 12 (buprenorphine) with no stratification factors. Statisticians generated and sent the randomisation lists directly to the production and packing facilities without researcher involvement. Paracetamol and identical inert placebo tablets were purchased from Kragero Tablettproduksjon A/S, Norway. Mundipharma Research Limited, UK provided buprenorphine TDS and identical inert placebo. The patients, carers, clinicians, pharmacy, researchers and study statistician were masked to group identity until completion of the protocol.

### 2.4 Intervention

As shown in Table 1, participants without current scheduled analgesics or who received  $\leq 1 \text{ g}/\text{day}$  of paracetamol were allocated to step 1, oral paracetamol (increased to a maximum of  $3 \text{ g}/\text{day}$ , active or placebo). Participants who were already prescribed regular doses of  $> 1 \text{ g}/\text{day}$  of paracetamol, buprenorphine  $5 \mu\text{g}/\text{hour}$  or non-steroidal anti-inflammatory drugs (except low-dose acetylsalicylic acid) were allocated to step 2, buprenorphine TDS (maximum dose of  $10 \mu\text{g}/\text{hour}$ , active or placebo). Patients with dysphagia, to whom it was not deemed feasible to administer oral tablets, were allocated to step 2 regardless of whether they were already using paracetamol.

We used a fixed-dose regimen throughout the 13-week treatment period: paracetamol  $1 \text{ g}$  tablet/placebo was administered at breakfast, lunch and dinner (approximately 8:00 a.m., noon, 6:00 p.m.) for a total daily dose of  $3 \text{ g}$  in the active group (corresponding to step 1; see Table 1). If the patient was using paracetamol  $\leq 1 \text{ g}/\text{day}$  prior to study inclusion, the study treatment was prescribed in addition to the basis dose, giving a maximum total dose of  $1 \text{ g}$  three times daily (supplement active or placebo) [step 1b; Table 1]. Buprenorphine/placebo TDS was changed weekly for a total dose of  $5 \mu\text{g}/\text{hour}$  in the active group (step 2a; Table 1). However, if the patient was using buprenorphine TDS  $5 \mu\text{g}/\text{hour}$  prior to study inclusion, the study treatment was administered as an additional  $5 \mu\text{g}/\text{hour}$  TDS (active or placebo) to yield a total dose of  $10 \mu\text{g}/\text{hour}$  in the active group (step 2b; Table 1). Patients who were unable to tolerate study treatment were withdrawn from the study and treated as clinically appropriate.

### 2.5 Concomitant Drugs

All participants continued their usual medical treatment after inclusion in the study (including any regular or 'as

**Table 1** Study treatment steps 1–2

Step	Regular analgesic treatment	Study treatment	Dose
1	No analgesics (1a) or paracetamol $\leq 1$ g/day (1b)	Paracetamol tablets Placebo tablets	Maximum 3 g/day Inert placebo
2	Non-opioid analgesics (paracetamol $> 1$ g/day, and/or NSAID), or no analgesics, but with difficulty swallowing tablets (2a), or buprenorphine 5 $\mu$ g/h (2b)	Buprenorphine TDS Placebo TDS	5 $\mu$ g/h (maximum 10 $\mu$ g/h in 2b) Inert placebo

NSAID non-steroidal anti-inflammatory drug, except low-dose acetylsalicylic acid, TDS transdermal system

needed' analgesic). The use of 'as needed' analgesics was allowed and monitored during the study, ensuring that all patients received adequate pain treatment irrespective of group allocation. Ongoing treatment with antidepressants, other psychotropic drugs and regular analgesics was allowed if the dose had remained stable for 4 weeks prior to study inclusion. Clinicians were advised to keep doses of psychotropic and analgesic drugs unchanged during the study period if possible. If lasting changes were made to regular analgesic treatment or antidepressants, the patient was withdrawn from the study. Lists of regular and 'as needed' prescriptions and documentation of administered doses were extracted from medical records at each visit.

## 2.6 Primary and Secondary Outcome Measures

Depressive symptoms were assessed using the CSDD scale, which has been validated and used in clinical studies including people with and without dementia [24]. Each of the 19 items is rated from zero (no symptoms) to two (severe symptoms), and yields a sum score of between zero (no depression) and 38 (most severe depression). While the CSDD scale alone cannot be used to accurately diagnose depression in dementia, it is useful as a screening tool and sufficiently precise to assess change in depressive symptom burden over time. Pain was assessed using the MOBID-2 Pain Scale, a two-part staff-administered behavioural instrument to assess pain in older persons with advanced dementia (see the Electronic Supplementary Material 1) [22]. The evaluation of inferred pain intensity is based on the patient's pain behaviours during standardised guided movements of different body parts (Part 1), and pain behaviours that might be related to internal organs, head and skin are recorded on an anatomical figure along with inferred pain intensity for each region to allow monitoring over time (Part 2). Excellent interrater and test-retest reliability, internal consistency and validity have been reported [22]. The tool has also demonstrated responsiveness to treatment, as it is able to detect change in the total score (range 0–10) after pain treatment has been initiated [22].

For subgroup analyses, mild/no pain was defined as MOBID-2  $< 3$  and moderate/severe pain as MOBID-2  $\geq 3$ . To assess cognitive function at inclusion, we used the MMSE as a screening tool, with MMSE scores of 0–10 defined as severe and MMSE scores of 11–20 defined as moderate dementia [25]. Although the MMSE scale poorly distinguishes between patients with no/questionable dementia, it has shown high agreement with the Clinical Dementia Rating scale for the staging of moderate and severe dementia using these cut-off scores [25]. Assessments of depression (CSDD) and pain (MOBID-2) were made at baseline and 6 and 13 weeks. Adverse events and tolerability were monitored and recorded at each visit. The primary outcome was the effect of analgesic treatment on change in depressive symptoms (CSDD) from baseline to 13 weeks. Secondary outcomes were the effect of analgesic treatment (paracetamol or buprenorphine) on change in pain (MOBID-2) from baseline to 13 weeks, and adverse events and dropout from treatment.

## 2.7 Sample Size

As a preliminary sample size estimate, we used results from Banerjee et al., who found in their updated power analyses that approximately 260 participants would be required to provide 90% power to detect a 2-point difference in the CSDD scale (standard deviation 5; standardised effect size 0.4) between two groups (active and placebo treatment), allowing for 15% dropouts [5]. This estimate was used as a preliminary goal, when inclusion and dropout rates were unknown, and was reviewed when the first 113 patients had completed our 13-week trial protocol (or dropped out). We calculated our revised sample size using a sample size formula for longitudinal data because we have data with repeated measurements. We used a sample size formula for a longitudinal continuous response, where the correlation between repeated measurements (intra-cluster correlation) is taken into account, with the purpose to estimate the intervention effect on average over the total follow-up period [26]. This formula applies for group

comparisons with longitudinal data, such as randomised controlled trials. The same parameters (standard deviation 5, standardised effect size 0.4, 90% power,  $p < 0.05$ ) were used in the revised calculation, but based on available data from the first 113 patients, we were able to estimate the correlation coefficient of repeated measurements within individuals (intra-cluster correlation) with greater precision in the revised sample size calculation (intra-cluster correlation 0.25). The final estimate required 66 patients in each group to obtain 90% power to detect a 2-point CSDD difference. Adjusting for 20% dropouts, our final aim was to include 165 participants in total.

## 2.8 Statistical Analysis

Baseline characteristics were described as mean (standard deviation) for continuous variables, and with the number of patients and percentages of the sample size for categorical variables. Differences in adverse outcomes (deaths) between active treatment and placebo were assessed using the Pearson  $\chi^2$  test for categorical variables. Treatment effects on both the primary outcome (depression assessed by the CSDD) and the secondary outcome (pain assessed by the MOBID-2 Pain Scale) were assessed separately using linear mixed-effects models, which incorporated all assessments at baseline, 6 and 13 weeks. We treated time as a categorical variable, and included fixed effects for time, intervention and their interaction in the models. To account for clustering, the models were fitted with random intercepts for nursing home units and patients. Treatment effects were calculated for active treatment vs. placebo, these analyses were repeated with the use of other analgesics or antidepressants at baseline as covariates to control for any impact of concomitant drug use. We also conducted pre-planned subgroup analyses for paracetamol tablets compared with placebo tablets, buprenorphine TDS compared with placebo TDS, and to investigate treatment effects stratified for level of cognitive function and for the presence of moderate-to-severe pain. We regarded  $p < 0.05$  as significant. All statistical analyses were conducted with STATA/IC 14 (Stata Corp LP, College Station, TX, USA).

## 3 Results

Figure 1 shows the trial profile, wherein each patient is categorised by the first exclusion criterion that was fulfilled, after which no further assessments were made. Table 2 shows group allocation and characteristics of the 162 included patients at baseline. In total, 39 patients (24.1%) reported adverse events (Table 3), most frequently in the active buprenorphine group of whom 23 (52%)

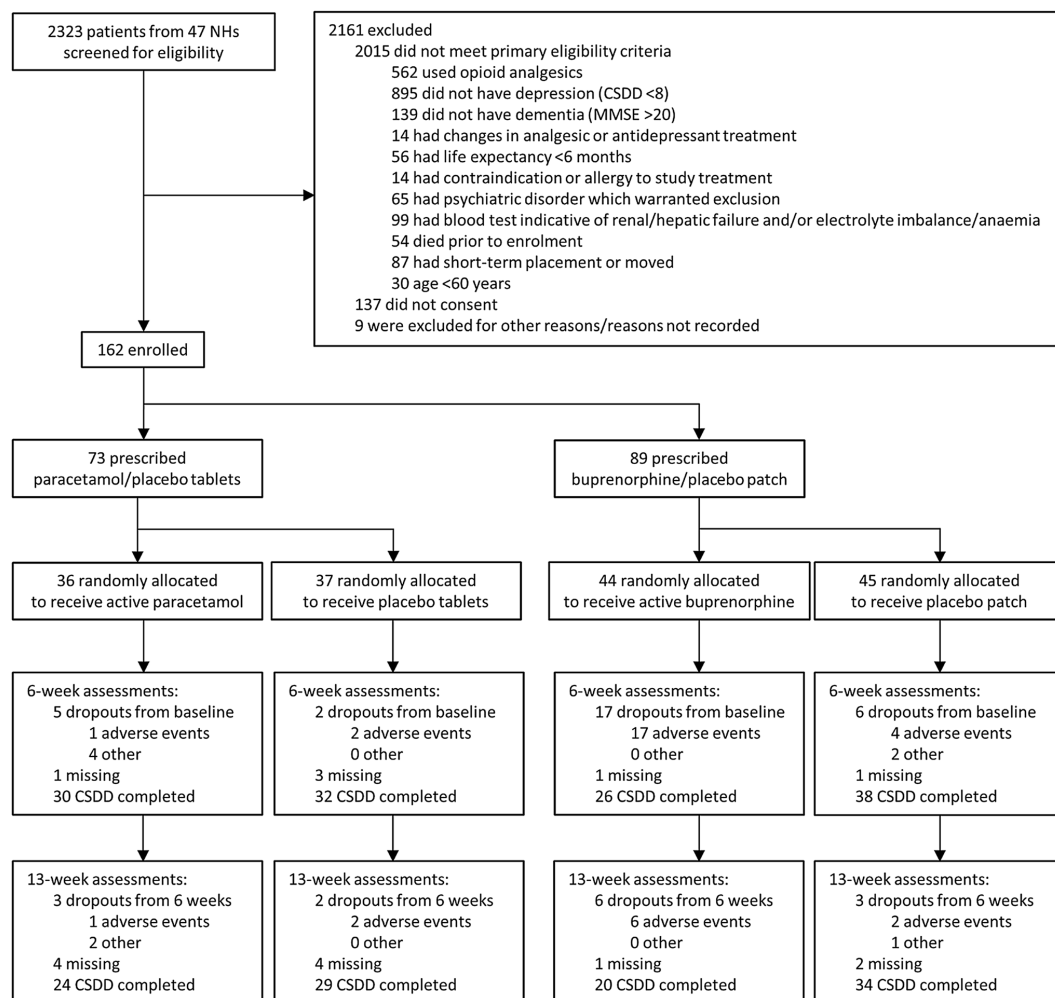
withdrew because of adverse events. Thirteen patients discontinued treatment owing to clinical deterioration or death; one in the paracetamol group, two who received placebo tablets, six in the buprenorphine group and four who received placebo TDS. Between-group differences in mortality were not statistically significant (Pearson  $\chi^2$  test;  $p = 0.447$ ).

From the linear mixed-model analysis (Table 4, Fig. 2), we found that the placebo group had a significant reduction in depressive symptoms (CSDD score) of  $-3.30$  (95% confidence interval  $-4.68$  to  $-1.92$ ) from baseline to the 13-week follow-up. The active treatment group did not have a significant CSDD change in the same period [mean change  $-0.66$  ( $-2.27$  to  $0.94$ )]. The estimated treatment effect from baseline to 13 weeks was  $2.64$  ( $0.55$ – $4.72$ ,  $p = 0.013$ ), thus receiving placebo was associated with a significant reduction in depressive symptoms from baseline to 13 weeks compared with those who received active treatment. The observed treatment effects were not affected by concomitant use of antidepressants or analgesics. Analysing patients in the different treatment groups separately, we found that neither active paracetamol nor buprenorphine had significant treatment effects on depressive symptoms from 0 to 13 weeks compared with placebo (Table 4, Fig. 2). The estimated treatment effects were  $1.98$  ( $-0.79$  to  $4.74$ ,  $p = 0.162$ ) for paracetamol vs. placebo tablets, and  $3.04$  ( $-0.11$  to  $6.19$ ,  $p = 0.059$ ) for buprenorphine vs. placebo TDS. Grouping patients according to whether they had moderate-to-severe pain at baseline did not yield significant treatment effects on depression compared with placebo; nor did separate analyses for patients with moderate and severe dementia (Table 4, Fig. 2).

There was no significant reduction in pain in the combined active treatment group (paracetamol and buprenorphine) compared with placebo (Table 5, Fig. 3). Active paracetamol was associated with a significant decrease in pain from 6- to 13-week assessments compared with placebo tablets, with an estimated treatment effect of  $-1.11$  ( $-2.16$  to  $-0.06$ ,  $p = 0.037$ ). This effect was not observed for active buprenorphine [coefficient  $0.26$  ( $-1.06$  to  $1.59$ ),  $p = 0.697$ ].

## 4 Discussion

This is the first placebo-controlled study investigating the efficacy of analgesic treatment for depressive symptoms in people with moderate-to-severe cognitive impairment and dementia. We have found that a stepwise increase of analgesic treatment, using either paracetamol tablets or buprenorphine TDS, was not effective as a means of reducing depressive symptoms in these patients. Contrary



**Fig. 1** Trial profile. Each patient was categorised by the first exclusion criterion that was fulfilled, after which no more assessments were made. *CSDD* Cornell Scale for Depression in Dementia, *MMSE* Mini-Mental State Examination, *NHs* nursing homes

to our initial hypothesis, we found that the placebo group had a significant decrease in depressive symptoms from baseline to the 13-week follow-up compared with the active treatment group. We did not find an overall benefit of active treatment on pain compared with placebo, but paracetamol reduced pain significantly from 6 to 13 weeks compared with placebo tablets (Table 5). Despite this, depressive symptoms did not decrease in the same group (Table 4).

While our results appear to indicate the reverse effect: a significant decrease in depressive symptoms in the placebo group compared with the active treatment group, this result

must be interpreted with caution for several reasons. This study includes people with severe dementia, in whom symptoms of both pain and depression are difficult to assess. We excluded patients in whom severe pain (MOBID-2  $\geq 8$ ) was identified because it would be unethical to risk prolonged untreated pain by randomising these patients to receive active treatment or placebo, and recommended instead that the responsible physician should initiate appropriate analgesic treatment.

Therefore, our results may not be generalisable to nursing home patients with dementia and severe pain. Most of the included patients were unable to self-report pain

**Table 2** Demographic and clinical characteristics of included patients at baseline

	Total (n = 162)	Placebo (n = 82)	Active (n = 80)
Age (y)	85.6 ± 7.4	86.2 ± 6.0	85.0 ± 8.7
Sex (female)	122 (75.3)	63 (76.8)	59 (73.8)
MMSE	7.8 ± 5.8	7.6 ± 5.7	8.0 ± 5.9
MOBID-2	2.7 ± 2.1	3.0 ± 2.3	2.4 ± 1.9
CSDD	11.2 ± 3.7	11.7 ± 4.1	10.8 ± 3.1
NPI-NH total score	32.1 ± 19.8	31.0 ± 20.1	32.8 ± 19.4
NPI-NH depression	4.4 ± 3.8	4.0 ± 3.7	5.0 ± 4.0
Analgesic	81 (50.0)	41 (50.0)	40 (50.0)
Antidepressant	81 (50.0)	50 (61.0)	31 (38.8)
Step 1a <sup>a</sup>	68	37	31
Step 1b <sup>b</sup>	5	0	5
Step 2a <sup>c</sup>	74	38	36
Step 2b <sup>d</sup>	15	7	8

Numbers represent mean ± standard deviation or number of patients (%)

CSDD Cornell Scale for Depression in Dementia, MMSE Mini-Mental State Examination, MOBID-2 Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, NPI-NH Neuropsychiatric Inventory-Nursing Home version

<sup>a</sup>Study treatment: paracetamol 1 g/placebo tablet three times daily

<sup>b</sup>Study treatment: paracetamol 1 g/placebo tablet two times daily + usual treatment: paracetamol ≤ 1 g/day

<sup>c</sup>Study treatment: buprenorphine 5 µg/h/placebo transdermal system

<sup>d</sup>Study treatment: buprenorphine 5 µg/h/placebo transdermal system + usual treatment: buprenorphine 5 µg/h transdermal system

**Table 3** Adverse reactions that may be related to study treatment

	Placebo tablets (n = 37)	Paracetamol (n = 36)	Placebo TDS (n = 45)	Buprenorphine TDS (n = 44)	All patients (n = 162)
Patients with adverse reactions <sup>a</sup>	4 (10.8%)	2 (5.6%)	8 (17.8%)	25 (56.8%)	39 (24.1%)
Gastrointestinal	0	0	0	7	6
Neurological	0	0	2	12	14
Dermatological	0	0	1	0	1
Psychiatric	0	0	0	17	17
Infection	1	0	0	1	2
Falls/fractures	1	1	1	4	7
Major clinical changes, including hospitalisation/death	2	1	4	7	14

TDS transdermal system

<sup>a</sup>Each patient may have had several reported reactions

reliably because of advanced cognitive impairment. Although proxy-rated pain is the best available pain assessment method in this group, we have no method to ascertain the patients' subjective pain experience. In patients with very limited verbal and non-verbal expression, pain intensity may be underestimated by proxy rating. Our initial hypothesis was therefore that undiagnosed and therefore untreated painful symptoms may cause

exacerbated depressive symptoms in people with advanced dementia.

The CSDD scale has been developed for use in people with dementia, and has shown good sensitivity and specificity. However, as noted in a recent systematic review and meta-analysis, most studies that have tested the scale have excluded people with severe dementia or communication deficits, thus limiting the majority of the evidence to people

**Table 4** Estimated effect of active analgesic treatment on primary outcome (Cornell Scale for Depression in Dementia depressive symptoms) compared with placebo; mixed-model analysis including exploratory subgroup analyses

	<i>N</i>	From baseline to 13 wk			From baseline to 6 wk			From 6 to 13 wk		
		<i>C</i>	(95% CI)	<i>P</i> value	<i>C</i>	(95% CI)	<i>P</i> value	<i>C</i>	(95% CI)	<i>P</i> value
Primary analysis										
All patients	160	2.64	(0.55–4.72)	0.013	0.74	(–1.03 to 2.52)	0.411	1.89	(–0.29 to 4.08)	0.090
Stratified on cognition										
MMSE 11–20	49	2.24	(–1.24 to 5.72)	0.207	0.33	(–2.50 to 3.16)	0.818	1.91	(–2.05 to 5.86)	0.344
MMSE 0–10	92	1.10	(–1.49 to 3.69)	0.405	0.56	(–1.75 to 2.86)	0.635	0.54	(–2.27 to 3.35)	0.705
Stratified on drug type										
Paracetamol/placebo tablets	73	1.98	(–0.79 to 4.74)	0.162	0.40	(–2.39 to 3.18)	0.780	1.58	(–1.49 to 4.64)	0.313
Buprenorphine/placebo TDS	89	3.04	(–0.11 to 6.19)	0.059	0.96	(–1.45 to 3.37)	0.433	2.07	(–1.06 to 5.20)	0.194
Stratified on pain level										
MOBID-2 < 3	57	2.65	(–0.49 to 5.80)	0.098	1.42	(–1.00 to 3.83)	0.251	1.24	(–1.40 to 3.87)	0.357
MOBID-2 ≥ 3	103	2.25	(–0.55 to 5.04)	0.115	0.47	(–1.98 to 2.91)	0.709	1.78	(–1.31 to 4.88)	0.260
MOBID-2 ≥ 3 and paracetamol	47	1.63	(–2.68 to 5.94)	0.459	–0.38	(–4.51 to 3.76)	0.858	2.01	(–2.52 to 6.53)	0.385
MOBID-2 ≥ 3 and buprenorphine	61	2.19	(–1.35 to 5.73)	0.226	1.32	(–1.87 to 4.51)	0.418	0.87	(–2.84 to 4.58)	0.646

*C* coefficient for time × treatment interaction, *CI* confidence interval, *MMSE* Mini-Mental State Examination, *MOBID-2* Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale, *N* number of patients with at least one valid assessment, *TDS* transmucosal system. See also the Electronic Supplementary Material 2, which reports all corresponding coefficients for change

with mild-to-moderate dementia [24]. In cognitively intact populations, the efficacy of pharmaceutical therapies for both depression and pain is difficult to isolate from expectation effects, including both placebo and nocebo effects [27]. Although people with advanced dementia may have a diminished or absent placebo response [28], the proxy raters are prone to observer bias such as the Hawthorne effect, which could potentially skew the observed difference between the treatment groups. Furthermore, we did not assess raters' expectation of group allocation, a factor that has been shown to interfere strongly with observed effects in placebo-controlled trials [27]. As shown in the first graph of Fig. 2, all patients had a trend towards decreasing severity of depressive symptoms from baseline to the 6-week follow-up. Similarly, Fig. 3 shows that pain tended to decrease from baseline to the 6-week follow-up, regardless of group allocation. This initial improvement across all groups exaggerates the apparent benefit of placebo on depressive symptoms, and may be caused by observer bias. Similar trends have been shown in other studies [5, 16].

The high dropout rate observed in the group receiving active buprenorphine may reduce comparability between active treatment and placebo conditions, but represents an important finding as it suggests lower than expected tolerability in this population, which warrants further investigation. In active treatment, only 44 of the 66 planned for in the final power analysis completed 13-week assessments. This may further limit our ability to detect a positive effect of treatment compared with placebo. However, our data are significantly in favour of the placebo condition ( $p = 0.013$ ), probably because the obtained mean CSDD difference of 2.64 at 13 weeks was larger than the threshold for a clinically relevant difference of 2.0 (standardized effect size 0.4) used in the power analysis. This means that the sample size was sufficient to explore our primary aim, and may indicate that adverse effects of active treatment led to apparent worsening of depressive symptoms. Known adverse effects of buprenorphine include symptoms such as sedation, reduced appetite and anxiety, which may overlap with items assessed by the CSDD scale and possibly be interpreted as increased depression. Secondary analyses, in

which patients were grouped based on the presence of moderate-to-severe pain, cognitive status and choice of analgesic treatment all show a similar trend in favour of the placebo condition, although these associations did not reach significance, probably because the sample size did not provide sufficient power for subgroup analyses.

An important limitation to the interpretation of our results is therefore that we do not have a sufficient sample size to determine whether there was a significant differential effect between paracetamol and buprenorphine on depressive symptoms. Furthermore, the extensive list of exclusion criteria was necessary to include this frail population in the current trial, but also limits the generalisability of our results to a more heterogeneous group of nursing home patients. A recent study found that patients with depression were more likely to be prescribed analgesic treatments [29]. This means that an unknown proportion of patients who theoretically may have benefited from the intervention were excluded from our study: 562 patients (38% of the 2323 patients screened) were excluded because of opioid analgesic use, without any further assessments of eligibility. This choice was made intentionally to assess treatment effects in patients who were not already using high doses of the study drugs, and in whom untreated pain was not identified as a primary clinical issue.

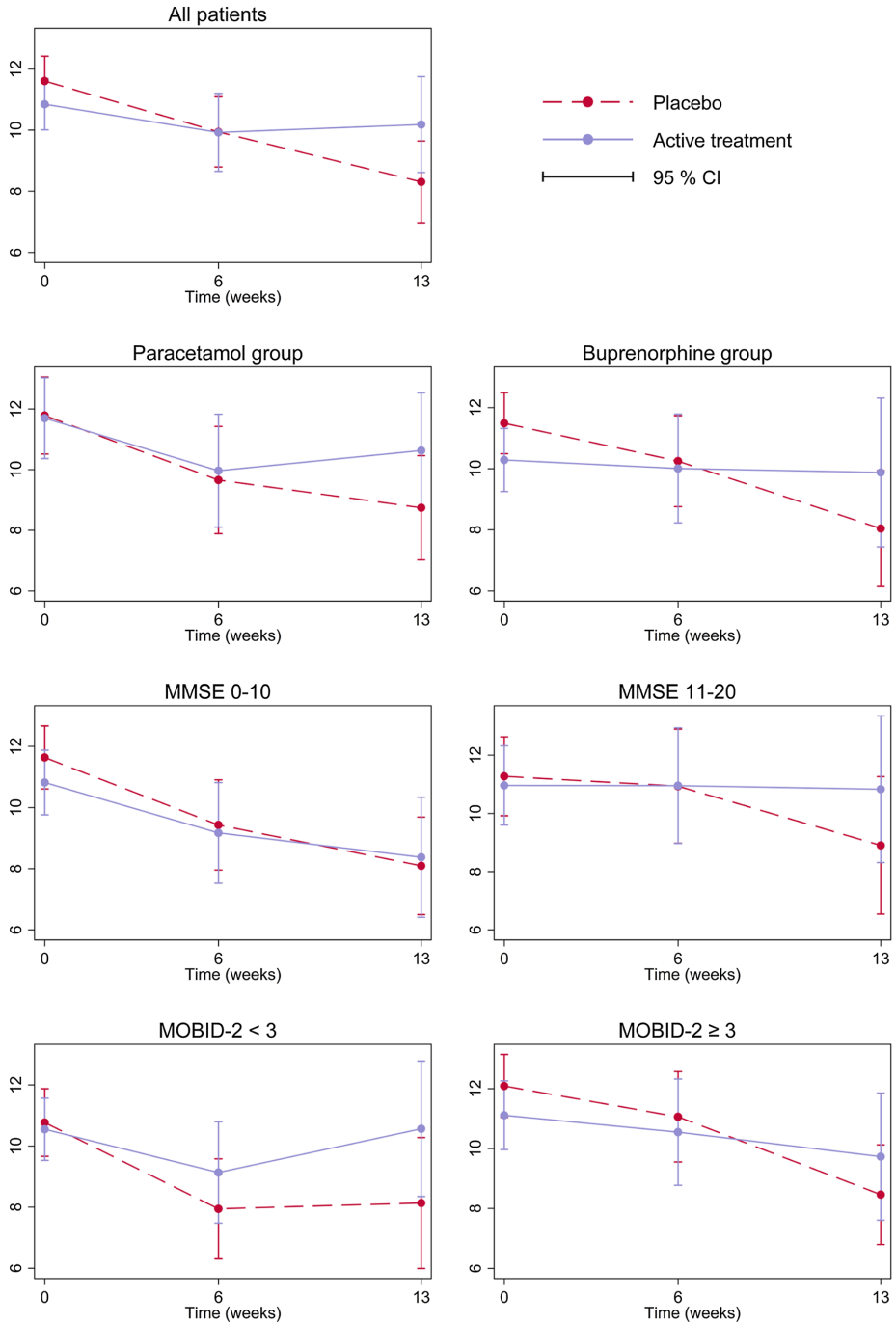
Several previous studies have suggested that depression in nursing home patients with cognitive impairment may be related to untreated pain. The association between pain and depression, also known as the pain-depression dyad, has been observed in nursing home patients at all stages of cognitive impairment [13, 14]. Secondary analyses from a previous cluster-randomised study, which assessed the efficacy of a stepwise increase in analgesic treatment for depressive symptoms in 175 nursing home patients with dementia and agitation, found a significant but small benefit on the mood syndrome cluster assessed with the Neuropsychiatric Inventory – Nursing Home version [16]. They included patients with agitation, whereas in our study depression was an inclusion criterion. Furthermore, a higher proportion of patients were allocated to receive paracetamol relative to our study [120 (69%) and 36 (45%), respectively]. They had an open-label design with the control group receiving usual care, consequently their results may have been biased owing to a Hawthorne effect. These methodological differences may in part explain our apparently opposing result.

Nonetheless, our rigorous placebo-controlled design justifies our conclusion that analgesic treatment alone is not sufficient to improve depressive symptoms in nursing home patients with dementia and depression in the absence of severe pain. By excluding patients with severe pain from the trial, we may have limited the potential to find

beneficial effects of analgesic treatment for depression. However, subgroup analyses stratified on pain level did not indicate that patients with moderate-to-severe pain had a more beneficial effect of active treatment on depressive symptoms. Although the group that received active paracetamol had a significant decrease in pain compared with those who received placebo tablets, there was a trend towards more persistent depressive symptoms in this group during the same period. While the latter result was not statistically significant, it indicates that the negative result on the main outcome of the current trial cannot be explained by the absence of pain at baseline.

Importantly, no clear causal relationship between pain and increased depression, or between depression and increased pain, has been established. Pain and depression are known to mutually exacerbate each other, a relationship that may be most accurately characterised as multifactorial. Although many nursing home patients with depression have comorbid chronic pain, other associated problems such as isolation and lack of social contact or meaningful activity may be equally important [30]. In this perspective, it may not be surprising that an isolated pain intervention is insufficient to improve depressive symptoms. Rather, our results show that careful assessment of painful symptoms, followed by the implementation and continuous re-evaluation of appropriate interventions, is an absolute requirement for adequate care in this population, as both untreated pain and use of unnecessary analgesics may lead to harm. Patients with cognitive impairment are particularly susceptible to the adverse effects of analgesics and antidepressants, and may be unable to communicate verbally the severity of their symptoms. This makes it particularly challenging to ensure that the benefit of pharmacological treatment outweighs any potential harm.

A 2011 study found that physicians in Norwegian nursing homes rarely diagnosed depression before prescribing antidepressants, and that treatment with antidepressants often was continued despite great uncertainty of their effectiveness [31]. Forty percent of nursing home patients in Norway use antidepressants [32]. This is in line with the pooled percentage of antidepressant use in Western European nursing homes [1], and indicates that the need for improved prescribing practice is not exclusive to Norway. Future advances should go towards more comprehensive treatment strategies that include both pharmacological and non-pharmacological interventions, as exemplified by Chen and Lin [33]. Non-pharmacological interventions that have been shown to reduce depressive symptoms in dementia include caregiver education and engagement in physical activity and pleasant events, but more evidence is needed to determine which strategies are most effective [34, 35].





◀ **Fig. 2** Change in depressive symptoms (Cornell Scale for Depression in Dementia) throughout the study period. *CI* confidence interval, *MMSE* Mini-Mental State Examination, *MOBID-2* Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale

Buprenorphine elicits its pharmacological effects on the opioidergic system, but has previously been suggested as a potential agent for treatment-resistant depression as some patients have had promising results [18]. However, based on the high rate of adverse events and absence of benefit on depressive symptoms, it is unlikely that buprenorphine has any potential as a treatment for depression in nursing home patients with dementia. The efficacy and tolerability of buprenorphine TDS have not previously been investigated in people with dementia in a placebo-controlled study. Buprenorphine has similar pharmacokinetic properties and does not require dose adjustment in the elderly compared with younger patients [36]. In a study comparing healthy elderly people aged  $\geq 75$  years to those aged 50–60 years, buprenorphine TDS was found to have a slightly lower steady-state concentration with higher variability in the elderly group [37]. The same study found a lower rate of adverse events in the elderly subjects compared with the younger controls [37].

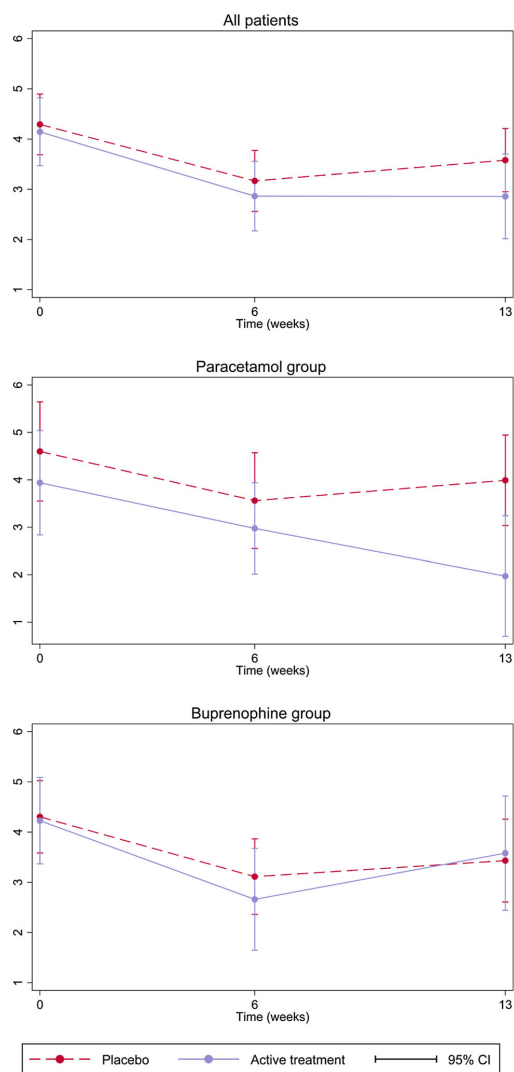
In the current study, the dropout rate owing to adverse events of buprenorphine exceeded that reported in a previous study of buprenorphine in patients with dementia [16], and is more than twice that reported in a study of opioid-naïve, cognitively intact elderly patients (aged  $\geq 75$  years), which found that 21% dropped out because of adverse events of buprenorphine [38]. This suggests that people with dementia may be more susceptible to adverse events of buprenorphine compared with elderly patients without cognitive impairment.

Because few large-scale safety studies of opioid analgesics in elderly patients exist, and none have included people with advanced dementia, we do not know whether this may represent a class effect of opioid analgesics or whether buprenorphine may be more poorly tolerated in frail elderly people and people with dementia compared with other opioid analgesics. In light of the widespread use of buprenorphine TDS and other opioid analgesics in nursing home patients, particularly in the oldest patients [39, 40], there is an urgent need for high-powered studies investigating the safety and efficacy of buprenorphine and other opioid analgesics for treating pain in people with advanced dementia.

**Table 5** Estimated effect of active analgesic treatment on secondary outcome [Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale (MOBID-2) pain intensity] compared with placebo; mixed-model analysis including exploratory subgroup analyses

	<i>N</i>	From baseline to 13 wk			From baseline to 6 wk			From 6 to 13 wk		
		<i>C</i>	(95% <i>CI</i> )	<i>P</i> value	<i>C</i>	(95% <i>CI</i> )	<i>P</i> value	<i>C</i>	(95% <i>CI</i> )	<i>P</i> value
Secondary analysis										
All patients	147	-0.19	(-1.02 to 0.64)	0.652	0.19	(-0.59 to 0.97)	0.634	-0.38	(-1.25 to 0.49)	0.389
Stratified on cognition										
MMSE 11–20	44	-1.01	(-2.44 to 0.41)	0.162	0.39	(-0.94 to 1.73)	0.563	-1.41	(-2.83 to 0.01)	0.051
MMSE 0–10	87	0.12	(-1.02 to 1.26)	0.838	0.03	(-1.05 to 1.11)	0.960	0.09	(-1.13 to 1.32)	0.884
Stratified on drug type										
Paracetamol/placebo tablets	69	-0.98	(-2.00 to 0.05)	0.061	0.14	(-0.83 to 1.10)	0.779	-1.11	(-2.16 to -0.06)	0.037
Buprenorphine/placebo TDS	78	0.47	(-0.77 to 1.71)	0.456	0.21	(-0.98 to 1.39)	0.733	0.26	(-1.06 to 1.59)	0.697
Stratified on pain level										
MOBID-2 $\geq 3$	90	-0.57	(-1.77 to 0.62)	0.347	-0.16	(-1.24 to 0.93)	0.779	-0.42	(-1.63 to 0.79)	0.498
MOBID-2 $\geq 3$ and paracetamol	38	-1.36	(-3.27 to 0.55)	0.164	0.07	(-1.67 to 1.82)	0.933	-1.43	(-3.25 to 0.39)	0.123
MOBID-2 $\geq 3$ and buprenorphine	52	0.23	(-1.32 to 1.77)	0.775	-0.38	(-1.81 to 1.05)	0.607	0.60	(-1.04 to 2.25)	0.474

*C* coefficient for time  $\times$  treatment interaction, *CI* confidence interval, *CSDD* Cornell Scale for Depression in Dementia, *MMSE* Mini-Mental State Examination, *N* number of patients with at least one valid assessment, *TDS* transdermal system. See also the Electronic Supplementary Material 3, which reports all corresponding coefficients for change



**Fig. 3** Change in pain intensity [Mobilisation-Observation-Behaviour-Intensity-Dementia-2 Pain Scale (MOBID-2)] throughout the study period in patients with moderate-to-severe pain at baseline (MOBID-2  $\geq$  3). *CI* confidence interval

## 5 Conclusion

Analgesic treatment did not reduce depression in patients with cognitive impairment and depressive symptoms. Patients who received active treatment had more persistent depressive symptoms than those who received placebo, possibly owing to adverse effects. These results point to the importance of continuous symptom assessment when

caring for people with dementia, ensuring that analgesics are given based on the correct indications with a minimal risk of harm, and using both pharmacological and non-pharmacological interventions as appropriate. Active buprenorphine was associated with high rates of adverse events, and should be prescribed cautiously in people with dementia.

**Acknowledgements** The authors thank the patients, their relatives and the nursing home staff for their willingness and motivation that made this work possible. Bettina S. Husebo would also like to thank the G.C. Rieber Foundation and the Norwegian Directorate of Health for supporting the authors' work at the Centre for Elderly and Nursing Home Medicine, University of Bergen, Norway. Parts of the work were carried out at the Biostatistics and Data analysis core facility (BIOS), University of Bergen.

**Author Contributions** All authors contributed significantly to the development of the study design, setting the aims, drafting the manuscript, and finalising this work.

### Compliance with Ethical Standards

**Funding** The DEP.PAIN.DEM trial and Ane Erdal and Elisabeth Flo are funded by the Research Council of Norway (sponsor's protocol code 221951). The DEP.PAIN.DEM trial has received a grant from the University of Bergen. Mundipharma Research Limited, UK provided study treatment.

**Conflict of interest** Clive Ballard has received consultancy honoraria from Acadia, Lundbeck, Heptares, Roche, Lilly, Otsuka, GSK, Pfizer and Synexus; speaker fees from Lundbeck, Lilly and Otsuka; and grant support from Acadia Pharmaceuticals 2014–2017. Ane Erdal, Elisabeth Flo, Dag Aarsland, Dagrun D. Slettebo and Bettina S. Husebo have no conflicts of interest directly relevant to the content of this article. The sponsors had no influence on the study design, data collection and analysis, decision to publish or preparation of the manuscript.

**Ethics approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Prior to enrolment, the trial was registered in ClinicalTrials.gov (NCT02267057), and was approved by the Norwegian Medicines Agency (EudraCT 2013-002226-23) and the Regional Committee for Medical and Health Research Ethics (REC-West 2013/1474).

**Consent to participate** Informed consent was obtained from all individual participants included in the study. Verbal and written informed consent was obtained in direct conversation with all patients who were deemed to have medical decision-making capacity. If participants did not have the capacity to give consent, the participant's next of kin or legal guardian provided informed consent in accordance with ethics committee requirements and Norwegian legislation at the time of the study. We expected that patients with Mini-Mental State Examination scores  $\geq$  16 would be able to give informed consent [41], but nevertheless we included the closest relatives of all patients in a discussion about consent and provided written information about the trial to ensure full transparency. To empower those patients with a reduced ability to consent, we attempted to adjust the information procedure to enable them to

understand the purpose and implications of study participation. We included a verbal and written statement assuring that their decision to give consent would not affect the quality of the medical care provided to the patient. Even though informed consent had been given, all participants were free to decline drug administration and other procedures at any time during the trial, irrespective of cognitive state.

**Open Access** This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

## References

- Janus SI, van Manen JG, IJzerman MJ, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *Int Psychogeriatr*. 2016;28(11):1775–90.
- Helvik AS, Engedal K, Benth JS, Selbaek G. Prevalence and severity of dementia in nursing home residents. *Dement Geriatr Cogn Disord*. 2015;40(3–4):166–77.
- Bergh S, Selbaek G, Engedal K. Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial. *BMJ*. 2012;344:e1566.
- Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry*. 2003;60(7):737–46.
- Banerjee S, Hellier J, Dewey M, Romeo R, Ballard C, Baldwin R, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet*. 2011;378(9789):403–11.
- Rosenberg PB, Drye LT, Martin BK, Frangakis C, Mintzer JE, Weintraub D, et al. Sertraline for the treatment of depression in Alzheimer disease. *Am J Geriatr Psychiatry*. 2010;18(2):136–45.
- Rabins PV, Blacker D, Rovner BW, Rummans T, Schneider LS, Tariot PN, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry*. 2007;164(12 Suppl.):5–56.
- Farina N, Morrell L, Banerjee S. What is the therapeutic value of antidepressants in dementia? A narrative review. *Int J Geriatr Psychiatry*. 2017;32(1):32–49.
- Nelson JC, Devanand DP. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J Am Geriatr Soc*. 2011;59(4):577–85.
- Sandvik RK, Selbaek G, Seifert R, Aarsland D, Ballard C, Corbett A, et al. Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: a cluster randomized trial. *Eur J Pain*. 2014;18(10):1490–500.
- Achterberg WP, Gambassi G, Finne-Soveri H, Liperoti R, Noro A, Fijters DH, et al. Pain in European long-term care facilities: cross-national study in Finland, Italy and The Netherlands. *Pain*. 2010;148(1):70–4.
- Hadjistavropoulos T, Herr K, Prkachin KM, Craig KD, Gibson SJ, Lukas A, et al. Pain assessment in elderly adults with dementia. *Lancet Neurol*. 2014;13(12):1216–27.
- Erdal A, Flo E, Selbaek G, Aarsland D, Bergh S, Slettebo DD, et al. Associations between pain and depression in nursing home patients at different stages of dementia. *J Affect Disord*. 2017;218:8–14.
- Leong IY, Nuo TH. Prevalence of pain in nursing home residents with different cognitive and communicative abilities. *Clin J Pain*. 2007;23(2):119–27.
- Chopra K, Arora V. An intricate relationship between pain and depression: clinical correlates, coactivation factors and therapeutic targets. *Expert Opin Ther Targets*. 2014;18(2):159–76.
- Husebo BS, Ballard C, Fritze F, Sandvik RK, Aarsland D. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. *Int J Geriatr Psychiatry*. 2014;29(8):828–36.
- van Ojik AL, Jansen PA, Brouwers JR, van Roon EN. Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids. *Drugs Aging*. 2012;29(8):615–25.
- Karp JF, Butters MA, Begley AE, Miller MD, Lenze EJ, Blumberger DM, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. *J Clin Psychiatry*. 2014;75(8):e785–93.
- Durso GR, Luttrell A, Way BM. Over-the-counter relief from pains and pleasures alike: acetaminophen blunts evaluation sensitivity to both negative and positive stimuli. *Psychol Sci*. 2015;26(6):750–8.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–98.
- Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. *Biol Psychiatry*. 1988;23(3):271–84.
- Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. *Eur J Pain*. 2014;18(10):1419–30.
- Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308–14.
- Goodarzi ZS, Mele BS, Roberts DJ, Holroyd-Leduc J. Depression case finding in individuals with dementia: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2017;65(5):937–48.
- Pernecky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry*. 2006;14(2):139–44.
- Twisk JWR. Applied longitudinal data analysis for epidemiology: a practical guide. 2nd ed. Cambridge: Cambridge University Press; 2013.
- Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol*. 2016;15(7):736–47.
- Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, et al. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain*. 2006;121(1–2):133–44.
- Gilmartin JF, Vaatainen S, Tormalehto S, Bell JS, Lonroos E, Salo L, et al. Depressive symptoms are associated with analgesic use in people with Alzheimer's disease: Kuopio ALSOVA study. *PLoS One*. 2015;10(2):e0117926.
- Snowden M, Sato K, Roy-Byrne P. Assessment and treatment of nursing home residents with depression or behavioral symptoms associated with dementia: a review of the literature. *J Am Geriatr Soc*. 2003;51(9):1305–17.
- Iden KR, Hjørleifsson S, Ruths S. Treatment decisions on antidepressants in nursing homes: a qualitative study. *Scand J Prim Health Care*. 2011;29(4):252–6.
- Gulla C, Selbaek G, Flo E, Kjøme R, Kirkevold O, Husebo BS. Multi-psychotropic drug prescription and the association to

- neuropsychiatric symptoms in three Norwegian nursing home cohorts between 2004 and 2011. *BMC Geriatr.* 2016;16(1):115.
33. Chen YH, Lin LC. Ability of the pain recognition and treatment (PRT) protocol to reduce expressions of pain among institutionalized residents with dementia: a cluster randomized controlled trial. *Pain Manag Nurs.* 2016;17(1):14–24.
  34. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ.* 2015;350:h369.
  35. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. *JAMA.* 2012;308(19):2020–9.
  36. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain.* 2009;13(3):219–30.
  37. Al-Tawil N, Odar-Cederlof I, Berggren AC, Johnson HE, Persson J. Pharmacokinetics of transdermal buprenorphine patch in the elderly. *Eur J Clin Pharmacol.* 2013;69(2):143–9.
  38. Karlsson J, Soderstrom A, Augustini BG, Berggren AC. Is buprenorphine transdermal patch equally safe and effective in younger and elderly patients with osteoarthritis-related pain? Results of an age-group controlled study. *Curr Med Res Opin.* 2014;30(4):575–87.
  39. Sandvik R, Selbaek G, Kirkevold O, Husebo BS, Aarsland D. Analgesic prescribing patterns in Norwegian nursing homes from 2000 to 2011: trend analyses of four data samples. *Age Ageing.* 2016;45(1):54–60.
  40. Jensen-Dahm C, Gasse C, Astrup A, Mortensen PB, Waldemar G. Frequent use of opioids in patients with dementia and nursing home residents: a study of the entire elderly population of Denmark. *Alzheimers Dement.* 2015;11(6):691–9.
  41. Etchells E, Darzins P, Silberfeld M, Singer PA, McKenny J, Naglie G, et al. Assessment of patient capacity to consent to treatment. *J Gen Intern Med.* 1999;14(1):27–34.

---

**Paper III**

# Tolerability of buprenorphine transdermal system in nursing home patients with advanced dementia: a randomized, placebo-controlled trial (DEP.PAIN.DEM)

Ane Erdal<sup>1</sup>  
 Elisabeth Flo<sup>2</sup>  
 Dag Aarsland<sup>3,4</sup>  
 Geir Selbaek<sup>5-7</sup>  
 Clive Ballard<sup>8</sup>  
 Dagrún D Slettebo<sup>1</sup>  
 Bettina S Husebo<sup>1,9</sup>

<sup>1</sup>Department of Global Public Health and Primary Care, Centre for Elderly and Nursing Home Medicine, University of Bergen, Bergen, Norway; <sup>2</sup>Department of Clinical Psychology, University of Bergen, Bergen, Norway; <sup>3</sup>Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; <sup>4</sup>Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway; <sup>5</sup>Centre for Old Age Psychiatric Research, Innlundet Hospital Trust, Ottestad, Norway; <sup>6</sup>National Advisory Unit on Aging and Health, Tønsberg, Norway; <sup>7</sup>Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway; <sup>8</sup>Exeter Medical School, University of Exeter, Exeter, UK; <sup>9</sup>Municipality of Bergen, Bergen, Norway

Correspondence: Ane Erdal  
 Department of Global Public Health and Primary Care, Centre for Elderly and Nursing Home Medicine, University of Bergen, Kalfarveien 31, PO Box 7804, Bergen N-5018, Norway  
 Tel +47 55 58 6036  
 Fax +47 55 58 6130  
 Email ane.erdal@uib.no

**Purpose:** Buprenorphine transdermal system is increasingly prescribed in people with advanced dementia, but no clinical trial has investigated the safety and factors associated with discontinuation due to adverse events in this population.

**Patients and methods:** One hundred sixty-two people with advanced dementia and significant depression from 47 nursing homes were included and randomized to active analgesic treatment (acetaminophen/buprenorphine) or identical placebo for 13 weeks. In this secondary analysis, the main outcomes were time to and reasons for discontinuation of buprenorphine due to adverse events. Change in daytime activity as measured by actigraphy was a secondary outcome.

**Results:** Of the 44 patients who received active buprenorphine 5 µg/hour, 52.3% (n=23) discontinued treatment due to adverse events compared to 13.3% (6 of 45) in the placebo group ( $p < 0.001$ ). Psychiatric and neurological adverse events were the most frequently reported causes of discontinuation (69.6%, n=16). Concomitant use of antidepressants significantly increased the risk of discontinuation (HR 23.2, 95% CI: 2.95–182,  $p = 0.003$ ). Adjusted for age, sex, cognitive function, pain and depression at baseline, active buprenorphine was associated with 24.0 times increased risk of discontinuation (Cox model, 95% CI: 2.45–235,  $p = 0.006$ ). Daytime activity dropped significantly during the second day of active treatment (–21.4%,  $p = 0.005$ ) and decreased by 12.9% during the first week ( $p = 0.053$ ).

**Conclusion:** Active buprenorphine had significantly higher risk of discontinuation compared with placebo in people with advanced dementia and depression, mainly due to psychiatric and neurological adverse events. Daytime activity dropped significantly during the first week of treatment. Concomitant use of antidepressants further reduced the tolerability of buprenorphine.

**Keywords:** opioids, analgesics, dementia, drug safety, adverse drug reactions

## Introduction

More than 80% of elderly people in long-term residential care have dementia.<sup>1</sup> Approximately 50% of these individuals suffer from pain of clinically significant intensity.<sup>2</sup> Cognitive impairment leads to difficulty in verbally expressing painful symptoms and complicates the assessment and treatment of pain.<sup>3</sup> This may increase the risk of untreated chronic pain in people with dementia compared with cognitively intact patients.<sup>4</sup> In the past few decades, systematic reviews have expressed concern that nursing home patients with dementia receive less analgesic treatment than those without dementia, despite comparable diagnoses of pain.<sup>5,6</sup>

Data from the entire population of Denmark in 2010 showed that 41% of the country's 42,291 nursing home patients used opioids, and that patients without dementia received significantly more opioid analgesics compared with those with dementia (43% and 38%, respectively).<sup>7</sup> A study including 425 patients from 12 nursing homes in Austria in 2011–2012 found that despite having more pain, fewer cognitively impaired patients received scheduled analgesic prescriptions compared with patients without cognitive impairment (36% and 58%, respectively).<sup>8</sup> Several studies have reported similar rates of analgesic use in nursing home patients with and without dementia,<sup>9,10</sup> with an overall increase in total analgesic use irrespective of cognitive state and a shift toward increased use of opioid analgesics.<sup>9</sup> In Norway, the use of opioid analgesics in nursing home patients increased from 11% in 2000 to 24% in 2011, with a substantial increase in the use of strong opioids from 1.9% to 17.9%.<sup>9</sup> In 2011, the odds ratio for the use of strong opioids in nursing home patients with dementia did not differ significantly compared with those without dementia.<sup>9</sup>

Buprenorphine transdermal system (TDS) has been recommended for elderly patients because of its favorable pharmacodynamic and pharmacokinetic profile, with low risk of serious adverse events.<sup>11</sup> Buprenorphine, a strong opioid, is a partial mu receptor agonist and a kappa receptor antagonist. This pattern of activity gives a ceiling effect for respiratory depression, without a clinically relevant ceiling effect on analgesia.<sup>12</sup> As one of few opioids, it does not require dose adjustment in renal insufficiency due to hepatic clearance.<sup>13</sup> Buprenorphine TDS is prescribed to over 10% of nursing home patients in countries where it is marketed, with estimated use in people with dementia ranging from 10.5% to 14.8%.<sup>7,9,10</sup> While buprenorphine TDS has shown high persistence rates in the general population, the rate of common adverse events such as nausea, dizziness, or sedation is higher than that of comparator opioids.<sup>14,15</sup> Dementia, age-related physiological changes, multimorbidity, frailty, and interactions with psychotropic drugs may impact the safety and tolerability of buprenorphine TDS.<sup>16</sup>

There is a well-documented association between pain and increased depressive symptoms in people with dementia,<sup>17</sup> and antidepressants have questionable efficacy for depression in these patients.<sup>18</sup> In a recent study, we investigated whether analgesic treatment with acetaminophen or buprenorphine TDS could improve depression in people with dementia. Contrary to our hypothesis, we found that active treatment was associated with more persistent depressive symptoms, and 52% of patients who received active buprenorphine

were withdrawn from the study due to adverse events during treatment.<sup>39</sup> Few studies have assessed the tolerability and adverse effects of buprenorphine TDS in nursing home patients with dementia, and none with a placebo-controlled design. Furthermore, buprenorphine may have additive or synergistic interaction effects with other drugs that have sedative effects. Elderly patients and people with dementia are particularly vulnerable to adverse effects such as sedation, but interactions between opioids and other commonly prescribed psychotropic drugs such as antidepressants have not been studied in this population. Similarly, anticholinergic drugs may negatively impact cognition in people with dementia, but we do not know whether high anticholinergic drug burden is associated with poorer tolerability of buprenorphine. There is a need to investigate clinically significant interactions between opioids and anticholinergic and psychotropic drugs in people with dementia.

In these secondary analyses of our study, the primary aim was to assess the tolerability of buprenorphine TDS in nursing home patients with moderate to severe dementia, controlling for pain intensity, depressive symptoms, cognitive state, and concomitant use of psychotropic and anticholinergic drugs. Secondary aims were to assess which adverse effects most frequently caused discontinuation and to determine how daytime activity changed during the first week of treatment.

## Patients and methods

### Study design and population

The current study comprises secondary analyses of data collected in the randomized, placebo-controlled trial “Efficacy of analgesic treatment for depression in nursing home patients with dementia (DEP.PAIN.DEM),” which was conducted in 47 nursing homes in 10 municipalities of Norway, including people with dementia (Mini-Mental State Examination [MMSE]  $\leq 20$ ) and depression (Cornell Scale for Depression in Dementia [CSDD]  $\geq 8$ ; full inclusion and exclusion criteria are presented in Table 1). The intervention consisted of a stepwise increase in analgesic treatment, and patients who did not use scheduled analgesics at baseline or used acetaminophen  $\leq 1$  g/day were prescribed acetaminophen in a total dose of 1 g three times daily. Patients who already used acetaminophen  $> 1$  g daily, nonsteroidal anti-inflammatory drugs (except low-dose acetylsalicylic acid), or buprenorphine 5  $\mu$ g/hour, or who had difficulty swallowing tablets, were prescribed buprenorphine TDS 5  $\mu$ g/hour in addition to their regular treatment and randomized to receive active treatment or placebo for 13 weeks with no further dose

**Table 1** Inclusion and exclusion criteria

Type of criterion	Patient characteristics
Inclusion criteria	Age $\geq 60$ years Long-term nursing home placement with $>4$ weeks' stay Dementia (MMSE $\leq 20$ ) Depression (CSDD $\geq 8$ , $>3$ weeks' duration)
Exclusion criteria	Life expectancy $<6$ months Severe medical disease that could interfere with study participation Impaired liver function, assessed by elevated serum alanine aminotransferase Severe renal impairment with serum creatinine indicative of eGFR $\leq 30$ (Cockcroft–Gault equation) Anemia (Hb $<8.5$ mmol/L for men, $<7.5$ mmol/L for women) or electrolyte imbalance (Na <sup>+</sup> , K <sup>+</sup> ) History of severe psychiatric disease prior to dementia onset Suicide risk (any attempts during the last year) Severe aggression (NPI-NH aggression item score $\geq 8$ , with aggression as the predominant symptom) Severe pain (MOBID-2 $\geq 8$ ) Uncontrolled epilepsy Contraindication or clinically significant drug interaction to the assigned study treatment Regular use of any opioid analgesic other than or exceeding buprenorphine 5 $\mu\text{g}/\text{hour}$ Cognitive impairment related to diagnoses other than Alzheimer's disease, frontotemporal dementia, vascular dementia, dementia with Lewy bodies, or mixed dementia

**Abbreviations:** CSDD, Cornell Scale for Depression in Dementia; eGFR, estimated glomerular filtration rate; MMSE, Mini-Mental State Examination; MOBID-2, Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale; NPI-NH, Neuropsychiatric Inventory-Nursing Home Version.

adjustment.<sup>39</sup> Patients who received buprenorphine/placebo TDS are included in the current analyses.

(EudraCT 2013-002226-23), and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02267057).

## Procedures

Clinicians were advised to keep doses of psychotropic and analgesic drugs unchanged during the study period, if possible. If lasting changes were made to regular analgesic treatment or antidepressants, the patient was withdrawn from the study. The study treatment was prescribed in addition to any regular or as-needed analgesics. In mild to moderate acute pain, patients were given as-needed analgesics in addition to study treatment, and the number of doses given during the study period was recorded. Patients with severe pain at baseline were excluded because it would be unethical to risk treating them with a placebo. We therefore ensured that the included patients would not suffer from prolonged or unnecessary untreated pain because of the study protocol. Furthermore, the physician who was responsible for the patient had full authority to discontinue study treatment promptly if clinical changes necessitated treatment with a known dose of active analgesic. Written informed consent was obtained from patients with medical decision-making capacity, or written presumed consent was obtained from a legally authorized representative in those with reduced capacity to consent in accordance with ethics committee requirements and current Norwegian legislation. The trial was approved by the Regional Committee for Medical and Health Research Ethics (REC-West 2013/1474) and the Norwegian Medicines Agency

## Randomization and masking

The trial was double blinded, and participants were randomly allocated to each arm in a 1:1 ratio according to computer-generated random numbers in blocks of 12 with no stratification factors. Buprenorphine TDS and identical, inert placebo (Mundipharma Research Limited, Cambridge, UK) were packed and marked indiscernibly, identifiable only by pack number. Patients, nursing home staff, physicians, pharmacy, researchers, and statisticians were all masked to group identity until completion of the analyses.

## Assessments

Assessments were made by the researchers in collaboration with the nursing home staff and included scheduled assessments at baseline, 6 and 13 weeks in addition to any spontaneous reports during the whole 13-week period. The tolerability of buprenorphine TDS was operationalized by assessing how many patients discontinued treatment due to adverse events (defined as suspected adverse event, clinical deterioration, or death) and how long treatment lasted before such discontinuation. Discontinuation for other reasons, such as protocol violation, was not included in the analysis, and in the following, "discontinuation" refers only to those cases defined here as caused by adverse events. To ensure that all suspected adverse events were reported, the proxy rater received standardized detailed verbal and written information



about known possible adverse effects of buprenorphine. They were instructed to pay attention to and report changes in any of the symptoms listed as potential adverse events, as well as any other clinical changes that occurred during treatment. If any clinical changes were observed during treatment, the raters were instructed to contact the researchers by phone immediately to report the symptoms. This information was distributed to other staff members, along with instructions to contact the researchers by phone immediately upon suspicion of any adverse event. In addition, the researchers asked specifically whether any adverse events were suspected at other contacts with the nursing home staff and during scheduled follow-up at 6 and 13 weeks of treatment. All suspected adverse events, irrespective of whether the patient discontinued treatment, were recorded verbatim as reported by nursing home staff, in as much detail as possible, including information about time from initiation to presenting symptoms and discontinuation of treatment.

Demographic information and a complete list of scheduled drug prescriptions (excluding prescriptions given *pro re nata*, ie, “as needed”) were extracted from the patients’ medical records at baseline. The total number of scheduled drug prescriptions was counted. Analgesic use was assessed by counting the number of prescriptions for drugs classified as systemic analgesics (Anatomical Therapeutic Chemical [ATC] code N02 or M01A). In addition, the individual and total numbers of scheduled psychotropic drugs were counted (antidepressants [N06A], anti-dementia [N06D], antipsychotic [N05A], anxiolytic [N05B], hypnotic and sedative [N05C], and antiepileptic [N03A] drugs). The total anticholinergic cognitive burden (ACB) was calculated by assigning 1 point for each prescribed drug with mild anticholinergic properties, 2 points for each drug with moderate anticholinergic effects, and 3 points for each drug with strong anticholinergic properties.<sup>19,20</sup> Between-group differences in drug use and morbidity at baseline were assessed by counting the number of prescriptions for drugs within each ATC group (A–V).

Activity was assessed by actigraphy registration using the Philips Actiwatch Spectrum, which was worn on the patients’ dominant or mobile wrist continuously for 14 days (7 days before and 7 days after treatment was started).<sup>21,22</sup> Total activity counts per day (Total AC) and mean intensity of activity per minute (AC/minute) for daily 12-hour intervals (09:00–21:00) were extracted from the Respironics Actiware 6.0.9 software. Mean activity counts for Total AC and AC/minute were calculated for both 7-day periods in all patients with at least 5 valid days of actigraphy recording per week.

Cognitive function was assessed using the MMSE, a 30-item questionnaire administered directly to the patient covering 11 domains (registration, orientation to time and place, short-term recall, attention, calculation, long-term recall, naming, repetition, comprehension [verbal and written], writing, and visuospatial construction) to yield a sum score from 0 (most severe impairment) to 30 (no impairment).<sup>23,24</sup>

Pain was assessed using the Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale (MOBID-2), a two-part staff-administered instrument to assess pain in people with advanced dementia.<sup>25</sup> The proxy evaluation of inferred pain intensity is based on the patient’s pain behaviors during standardized, guided movements of different body parts (Part 1), and pain behaviors that might be related to internal organs, head, and skin are recorded on an anatomical figure along with the inferred pain intensity for each region to allow monitoring over time (Part 2). The scale yields a final score from 0 (no pain) to 10 (worst pain imaginable). Good interrater and test–retest reliability, internal consistency, and validity have been shown, and the MOBID-2 scale has also demonstrated responsiveness to change.<sup>25</sup>

Depressive symptoms were assessed using the CSDD, which is a validated and widely used screening tool for depression in people with dementia.<sup>26</sup> It is administered by an interview with a proxy rater who is familiar with the patient, and it contains 19 items in five domains (mood-related signs, behavioral disturbance, physical signs, cyclic functions, and ideational disturbance). Each item is rated from 0 (no symptom) to 2 (severe symptoms) to yield a sum score of between 0 (no depression) and 38 (most severe depression).<sup>26</sup>

The main outcome measure was time to discontinuation of treatment due to adverse events. Secondary outcome measures were reasons for discontinuation, and change in total daytime activity and mean intensity of daily activity as measured by actigraphy recording.

## Sample size calculation

The DEP.PAIN.DEM trial was designed to obtain 90% power to detect a 2-point CSDD difference between active treatment (acetaminophen or buprenorphine) and identical placebo, with an SD of 5, a standardized effect size of 0.4,  $p < 0.05$ . The sample size was calculated using a sample size formula for longitudinal continuous response, adjusted for within-subject correlation between repeated measurements which was estimated to be 0.25 using data from the first 113 patients. One hundred thirty-two participants (66 in each group) were required, and adjusting for 20% dropouts, our final aim was to include 165 participants in total.<sup>39</sup>

## Statistical analysis

Baseline characteristics were described as mean and standard deviation for continuous variables, and with the number of patients and percentages of the sample size for categorical variables. Between-group differences were tested using independent-samples *t*-test for continuous variables with normal distribution; Mann-Whitney *U*-test for continuous variables with non-normal distribution; and Pearson's  $\chi^2$  test for categorical variables. We used a Kaplan–Meier survival plot and Cox regression models to determine whether patients who were randomized to receive active buprenorphine had a higher risk of discontinuation compared to those who received placebo. Cox regression analyses were repeated with age, sex, and MOBID-2, CSDD, and MMSE as covariates to determine which variables should be included in the adjusted analyses. To further assess whether the risk of discontinuation of active buprenorphine was modified by drug use, we tested the interaction between the treatment effect and each of the drug variables (total number of prescribed drugs, ACB score, total number of psychotropic drugs, and use of each class of psychotropic drugs [N06A, N06D, N05A, N05B, N05C, N03A]) on discontinuation, both unadjusted and adjusted for age, sex, and MOBID-2, CSDD, and/or MMSE at baseline if these covariates impacted discontinuation risk. We used cluster-robust variance estimates to account for dependence within nursing homes. To assess immediate changes in daytime activity during the early days of treatment, we used linear mixed-effects models for Total AC and AC/minute/day using the mean recording from the 7 days before treatment was initiated as baseline. Time was included as a categorical variable, with fixed effects for time, intervention, and their interaction in the models. The models were fitted with random intercepts for patients to account for correlation between longitudinal measurements, random slope for time, and residual error structure specified as independent by day. We regarded  $p < 0.05$  as significant. All statistical analyses were conducted with STATA/IC 15 (Stata Corp LP, College Station, TX, USA).

## Results

In total, 162 patients were included in the DEP.PAIN.DEM trial: 73 were prescribed acetaminophen/placebo tablets, and 89 patients were prescribed buprenorphine/placebo TDS and included in the current study. In the latter group, 44 were allocated to active treatment (hereafter, “active group”), and 45 to placebo (hereafter, “placebo group”; see Figure 1). Characteristics of the included patients at baseline are shown in Table 2. The groups were comparable at baseline on all tested variables except that the active group received more drugs

in ATC group M (seven patients in active treatment and one patient in placebo;  $p=0.025$ ), and the placebo group received more drugs in ATC group N (mean number of prescriptions 2.2 [SD 1.6] in the active group and 3.2 [SD 1.7] in the placebo group;  $p=0.001$ ). From the latter ATC group, use of antidepressants and total number of psychotropic drugs were significantly higher in the placebo group; we also found significantly higher ACB in the placebo group (Table 2). Fifteen patients used buprenorphine TDS 5  $\mu\text{g}/\text{hour}$  prior to inclusion, eight of whom were allocated to receive active treatment.

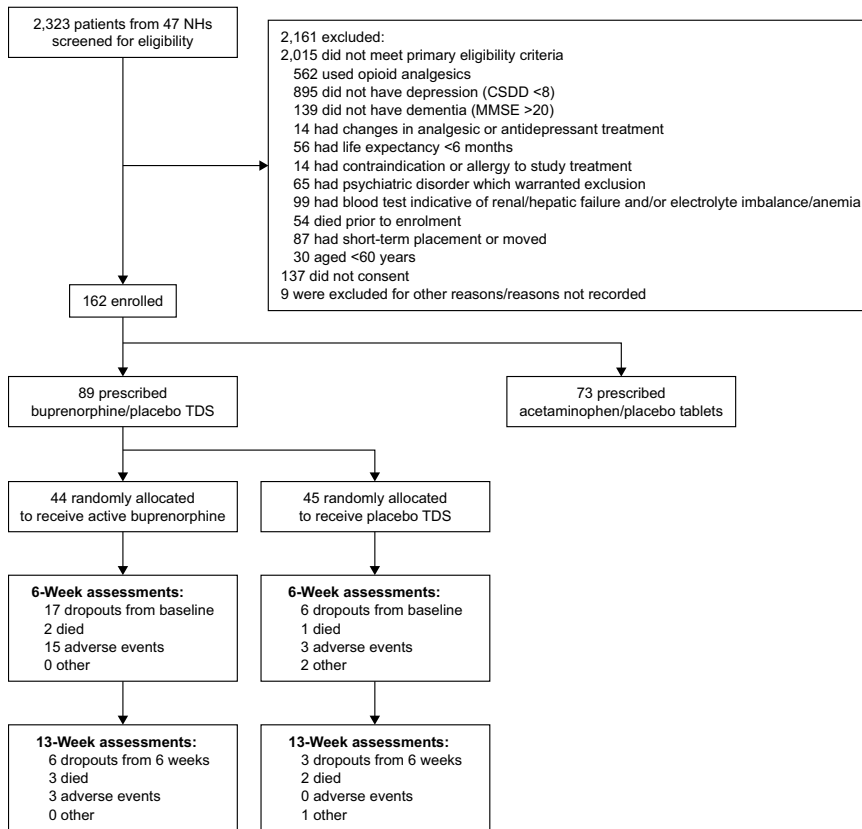
## Frequency and types of adverse events

All adverse events recorded are presented in Table 3. Because each patient may have had more than one adverse event of each type, the number of adverse events may not correspond to the number of patients affected unless specified. Psychiatric adverse events were reported most frequently, with 17 separate adverse effects recorded in the active treatment group and none in the placebo group ( $p=0.003$ ). Of psychiatric symptoms, personality changes (ie, changed emotional lability or other behavioral changes described as such) were the most frequent, reported in eight patients (18.2%), followed by confusion reported in five patients (11.4%). Neurological adverse events were the second most commonly reported, with 11 adverse effects recorded in the active treatment group and 2 in the placebo group ( $p=0.039$ ). The most frequent neurological adverse event and the single most frequent adverse symptom was sedation/somnolence, which was reported in nine patients (20.5%) receiving active treatment and two patients receiving placebo (4.4%,  $p=0.022$ ).

## Rates and causes of discontinuation

Buprenorphine TDS active treatment was discontinued in 23 patients (52.3%) due to adverse events, compared with 6 patients (13.3%) in the placebo group ( $p < 0.001$ ). Mean time to discontinuation was 61 days (SD 36) in the active treatment group and 82 days (SD 24) in the placebo group. Within the first 14 days, nine patients (20.5%) discontinued active treatment, and two patients (4.4%) discontinued placebo. Nearly half of patients who did not tolerate active treatment reported several types of adverse events (Table 4). Psychiatric adverse events were the most frequent cause of discontinuation reported in 12 of 23 patients (52%). Neurological adverse events were the second most frequent cause of discontinuation reported in nine patients (39%), five of whom also had psychiatric symptoms.

Kaplan–Meier estimates of time to discontinuation are shown in Figure 2. Throughout the study, patients who



**Figure 1** Trial profile.

**Abbreviations:** CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; NH, nursing home; TDS, transdermal system.

**Table 2** Background characteristics of included patients at baseline

Characteristics	Total (n=89)	Active treatment (n=44)	Placebo (n=45)	p-value
Age <sup>a</sup>	85.8 (7.2)	85.6 (8.5)	86.0 (5.9)	0.782
Sex (female) <sup>b</sup>	67 (75.3%)	33 (75.0%)	34 (75.6%)	0.952
MMSE <sup>c</sup>	7.0 (6.1)	6.8 (5.6)	7.3 (6.5)	0.737
MOBID-2 <sup>a</sup>	3.1 (1.9)	2.7 (1.8)	3.5 (2.0)	0.095
CSDD <sup>a</sup>	10.9 (3.4)	10.3 (2.4)	11.5 (4.1)	0.099
Analgesics <sup>b</sup> (N02/M01A)	78 (87.6%)	37 (84.1%)	41 (91.1%)	0.314
Antidepressants <sup>b</sup> (N06A)	41 (46.1%)	14 (31.8%)	27 (60.0%)	0.008
Antipsychotics <sup>b</sup> (N05A)	20 (22.5%)	8 (18.2%)	12 (26.7%)	0.338
Anti-dementia drugs <sup>b</sup> (N06D)	17 (19.1%)	5 (11.4%)	12 (26.7%)	0.066
Anxiolytics <sup>b</sup> (N05B)	24 (27.0%)	9 (20.5%)	15 (33.3%)	0.171
Antiepileptics <sup>b</sup> (N03A)	9 (10.1%)	5 (11.4%)	4 (8.9%)	0.699
Sedatives/hypnotics <sup>b</sup> (N05C)	26 (29.2%)	9 (20.5%)	17 (37.8%)	0.072
Total number of psychotropics <sup>c</sup>	1.6 (1.3)	1.2 (1.1)	1.9 (1.3)	0.007
Anticholinergic drugs <sup>c</sup> (ACB)	1.4 (1.5)	0.9 (1.3)	1.8 (2.8)	0.014
Total number of drugs <sup>a</sup>	6.7 (3.0)	6.4 (3.5)	7.1 (2.5)	0.262

**Notes:** Numbers represent mean (SD) or number of patients (%). <sup>a</sup>Independent samples t-test. <sup>b</sup>Pearson's  $\chi^2$ -test. <sup>c</sup>Mann-Whitney U-test.

**Abbreviations:** ACB, anticholinergic cognitive burden; CSDD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale.

**Table 3** Adverse events that may be related to study treatment

	<b>Buprenorphine n=44</b>	<b>Placebo n=45</b>	<b>p-value<sup>a</sup></b>
Patients with reported adverse reactions <sup>b</sup>	25 (56.8%)	8 (17.8%)	<b>&lt;0.001</b>
Patients who discontinued treatment	23 (52.3%)	6 (13.3%)	<b>&lt;0.001</b>
Neurological	11	2	<b>0.039</b>
Sedation/somnolence	9 (20.5%)	2 (4.4%)	<b>0.022</b>
Seizure	1 (2.3%)	–	0.309
Loss of coordination	1 (2.3%)	–	0.309
Psychiatric	17	–	<b>0.003</b>
Personality changes	8 (18.2%)	–	<b>0.003</b>
Anxiety	1 (2.3%)	–	0.309
Agitation	2 (4.5%)	–	0.148
Confusion	5 (11.4%)	–	<b>0.020</b>
Hallucinations	1 (2.3%)	–	0.309
Gastrointestinal	6	–	0.117
Dry mouth	1 (2.3%)	–	0.309
Nausea	3 (6.8%)	–	0.075
Vomiting	1 (2.3%)	–	0.309
Anorexia	1 (2.3%)	–	0.309
Dermatological			
Application site rash	–	1 (2.2%)	0.320
Other	8	2	0.204
Fall	4 (9.1%)	1 (2.2%)	0.159
Fracture	1 (2.3%)	1 (2.2%)	<b>0.987</b>
Respiratory tract infection	1 (2.3%)	–	0.309
Hospitalization	2 (4.5%)	–	0.148
Deterioration/death	6 (13.6%)	4 (8.9%)	0.478

**Notes:** Bold figures indicate significantly different prevalence rates ( $p < 0.05$ ). <sup>a</sup>Pearson's  $\chi^2$ -test. <sup>b</sup>Each patient may have had more than one reaction.

received active treatment had 4.7 times higher risk of discontinuation compared with those who received placebo (Table 5; Cox proportional hazards model, unadjusted HR, 95% CI: 1.66–13.3,  $p=0.004$ ). Adjusted for age, sex, MOBID-2, CSDD, and MMSE at baseline, active treatment was associated with 24.0 times higher risk of discontinuation (95% CI: 2.45–235,  $p=0.006$ ). In this model, age, sex, depressive symptoms, and pain were not significantly associated with discontinuation (age: HR 1.0, 95% CI: 0.99–1.11,  $p=0.133$ ; sex: HR 0.32, 95% CI: 0.10–1.58,  $p=0.149$ ; CSDD: HR 1.1, 95% CI: 0.90–1.34,  $p=0.343$ ; MOBID-2: HR 1.1, 95% CI: 0.91–1.45,  $p=0.246$ ). Lower MMSE scores were associated with increased risk of discontinuation (HR 0.82, 95% CI: 0.71–0.94,  $p=0.005$ ), but interaction effects of MMSE score were tested in a new model and were not significant, that is, patients who received active treatment were not at increased risk of discontinuation if they had lower MMSE scores (HR 1.04, 95% CI: 0.82–1.31,  $p=0.767$ ).

### Drug use and rates of discontinuation

Total number of prescribed drugs, ACB score, total number of psychotropic drugs, and use of any individual psychotropic drug (N06A, N06D, N05A, N05B, N05C, or N03A; dichotomized) were all not independently associated with discontinuation of the study treatment (active or placebo). However, patients who received active treatment and used antidepressants had 21.6 times increased risk of

**Table 4** Symptom combinations reported in the 23 patients who discontinued active buprenorphine due to adverse events

Psychiatric	Neurological	Deterioration/death	Gastrointestinal	Fall
X				
X				
X				
X				
X			X	
X				X
X				X
X	X			
X	X			
X	X			
X	X			
X	X	X		
	X			
	X			
	X	X		
	X			
		X		
		X		
		X		
		X		
			X	
			X	
				X

Clinical Interventions in Aging downloaded from https://www.dovepress.com/ by 77.136.84.255 on 05-Jun-2018 For personal use only.

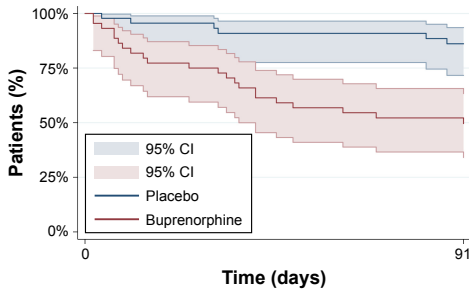


Figure 2 Kaplan-Meier survival plot: duration of study treatment.

discontinuation compared with patients who used antidepressants and received placebo (95% CI: 2.75–170,  $p=0.003$ ; Table 5). The interaction between active buprenorphine and antidepressant use remained unchanged when adjusting for age, sex, and MMSE (HR 23.2, 95% CI: 2.95–182,  $p=0.003$ ). In this model, active buprenorphine was not significantly associated with increased risk of discontinuation in patients who did not use antidepressants (HR 2.95, 95% CI: 0.53–16.6,  $p=0.218$ ), as shown in Figure 3 (Table 5). Interaction effects were calculated separately for each variable for drug use, and none except antidepressant use had significant interactions with active buprenorphine.

Although patients who used antidepressants and received active treatment had significantly increased risk of discontinuation, we were not able to detect any significant difference in the total number of adverse events and treatment discontinuations compared with those who did not use antidepressants. Nine of the 14 patients (64.3%) who received active treatment and used antidepressants reported adverse events and discontinued treatment. Of the 30 patients who received active treatment and did not use antidepressants, 16

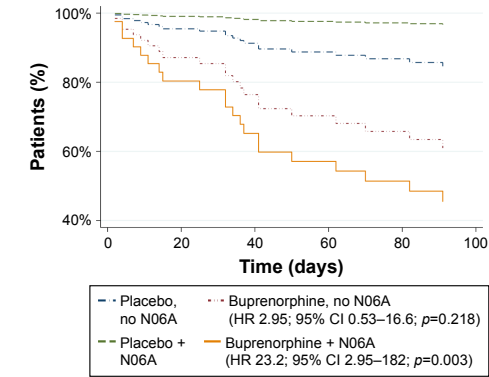


Figure 3 Cox proportional hazard plot: discontinuation risk stratified on treatment allocation and antidepressant use. Abbreviation: N06A, Antidepressant.

(53.3%) reported adverse events and 14 (46.7%) discontinued treatment. Using  $\chi^2$ -tests, the rates of adverse events and discontinuation in patients who received active treatment and used antidepressants were compared to those who did not use antidepressants (groups defined by the number of prescriptions for antidepressants at baseline), but no significant differences were found ( $p=0.599$  and  $0.419$ , respectively). We did not find that patients who used antidepressants reported any single type of adverse event more frequently, except confusion which was reported in three patients who used antidepressants (21.4%) and two patients who did not use antidepressants (6.7%,  $p=0.013$ ,  $\chi^2$ -test).

### Changes in activity during the first week of treatment

Day-to-day activity counts in the first week of treatment, measured by actigraphy, are shown in Figure 4 with the

Table 5 Estimated treatment effect of buprenorphine versus placebo on discontinuation (Cox regression)

	N	HR (95% CI)	p-value
Unadjusted	89	4.70 (1.66–13.3)	0.004
Model 1 <sup>a</sup>	76	7.19 (1.65–31.3)	0.009
Model 2 <sup>b</sup>	65	24.0 (2.45–235)	0.006
Modified by antidepressants <sup>c</sup>			
No antidepressants	89	1.88 (0.63–5.64)	0.257
Antidepressants	89	21.6 (2.75–170)	0.003
Modified by antidepressants <sup>d</sup>			
No antidepressants	76	2.95 (0.53–16.6)	0.218
Antidepressants	76	23.2 (2.95–182)	0.003

Notes: Modified analyses include interaction effects. <sup>a</sup>Adjusted for age, sex, and cognition (MMSE). <sup>b</sup>Adjusted for age, sex, cognition (MMSE), pain (MOBID-2), and depression (CSD). <sup>c</sup>Unadjusted.

Abbreviations: CSD, Cornell Scale for Depression in Dementia; MMSE, Mini-Mental State Examination; MOBID-2, Mobilization-Observation-Behavior-Intensity-Dementia-2 Pain Scale.

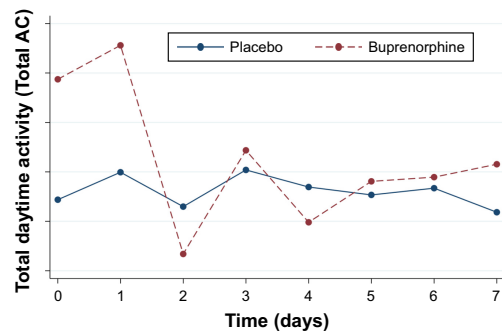


Figure 4 Daytime activity during the first week of study treatment. Notes: Actigraphy recording of total activity from 09:00 to 21:00 hours daily. Baseline score calculated as mean daily activity during the 7 days before treatment was started.

mean activity counts during the week before treatment started as the baseline activity score. Patients who received active treatment had significantly reduced daytime activity on day 2 of treatment compared with placebo (mixed model; Total AC:  $-16,967$ ,  $p=0.005$ ). This corresponds to a 21.4% decrease in total daytime activity in those who received active treatment. Comparing the mean daytime activity in the first week of treatment with baseline activity, we found that active treatment was associated with a 12.9% decrease in mean Total AC, but this effect was not statistically significant (mixed model;  $p=0.053$ ).

## Discussion

To our knowledge, this is the first placebo-controlled study investigating the tolerability and observed adverse events of buprenorphine TDS in nursing home patients with moderate to severe dementia. Patients who used antidepressants and received active treatment had the highest risk of discontinuation; this suggests a clinically relevant interaction between antidepressants and buprenorphine in people with dementia. Buprenorphine significantly reduced daytime activity as measured by actigraphy on the second day of treatment compared with placebo, supporting reports from nursing home staff of increased sedation/somnolence as the most frequent adverse effect. The poor tolerability of buprenorphine TDS due to the high risk of neurological and psychiatric adverse events should be considered carefully by clinicians before prescribing to people with dementia, and particularly to patients who are also using antidepressants, which may further reduce tolerability. This study does not assess the efficacy of buprenorphine TDS for treating different types of pain in dementia, which should be addressed in future research.

In the active treatment group, 57% had reported adverse events. A recent meta-analysis of six randomized controlled studies (five were placebo controlled) found that 82% of elderly patients ( $\geq 65$ ) had adverse events of buprenorphine TDS.<sup>27</sup> The lower rate of reported adverse events in our study can most likely be attributed to our reliance on proxy observations of adverse events. Although self-report of symptoms is considered the gold standard, people with advanced dementia often have impaired ability to reliably report their symptom burden. For example, less than half of patients with MMSE  $\leq 6$  are able to comprehend any assessment scale used to self-report painful symptoms.<sup>28</sup> In our study, mean MMSE was 7 at baseline; therefore, many could not self-report adverse effects of buprenorphine TDS. Mild adverse effects of buprenorphine are subjective, they may not be easily observable, and subtle changes such as reduced

appetite, confusion, or agitation could be misinterpreted as neuropsychiatric symptoms in dementia which may not be attributed to study treatment by the proxy raters. Because people with communication difficulty due to advanced dementia cannot be expected to reliably self-report mild adverse events, the true prevalence of adverse events is likely to have been underestimated in our study due to observer bias. Therefore, this should be interpreted as a tolerability study presenting adverse events associated with discontinuation of treatment, rather than the absolute frequency of adverse events in people with dementia.

Although very frail patients with short life expectancy were not included in the trial, sudden clinical deterioration is difficult to predict and must be expected to occur during an extended follow-up period in nursing home patients with advanced dementia, regardless of exposure to a clinical intervention. The number of patients who were withdrawn from the study because of severe clinical deterioration with short life expectancy did not differ significantly between the active treatment and placebo groups, and our sample size and follow-up period were not designed to investigate whether buprenorphine use may be associated with increased mortality. Adverse events were registered on suspicion, based on detailed reports of clinical changes from nursing home staff. Even though we did not assess the likelihood of causality between the study treatment and each reported adverse event, we conclude that the difference in the total number of adverse events between active treatment and placebo can likely be attributed to adverse effects of buprenorphine.

Previous studies indicate that buprenorphine TDS is well tolerated in elderly patients, with studies reporting similar or lower rates of adverse events in healthy elderly patients compared with younger controls.<sup>29-31</sup> In elderly patients without dementia, the most common adverse events associated with discontinuation of buprenorphine treatment are gastrointestinal – nausea (8.2%), vomiting (3.9%), and constipation (2.0%) – followed by neurological symptoms – dizziness (5.1%), somnolence (2.0%), and headache (2.0%).<sup>27</sup> In our study, psychiatric and neurological adverse effects were frequent, reported in 16 of patients who discontinued treatment (36.4%). Four patients (9.1%) who discontinued treatment had gastrointestinal symptoms. This indicates that psychiatric adverse events of buprenorphine may occur more frequently in people with dementia compared with cognitively intact elderly patients. As buprenorphine has similar pharmacokinetic properties in elderly patients including those with renal impairment,<sup>29,32</sup> this reduced tolerability is most likely explained by pharmacodynamic changes in people with dementia.<sup>33,34</sup>

Buprenorphine TDS is absorbed slowly, and it reaches active concentration after ~24 hours and steady state during the first 72 hours in young healthy patients.<sup>35</sup> Although pharmacokinetics have not been investigated in the very old and frail, buprenorphine TDS appears to be absorbed at a similar rate in people aged  $\geq 75$  years compared to a younger control group.<sup>29</sup> The largest drop in daytime activity observed in our study (recorded ~24–36 hours after administration) may therefore correspond to the first systemic exposure to buprenorphine. While the reduction in daytime activity during the first week of active treatment was not statistically significant, this was probably due to low sample size.

Depression is associated with the use of antidepressants in nursing home patients with dementia.<sup>17</sup> Because depression was an inclusion criterion, we may have selected patients who used more antidepressants relative to other psychotropic drugs. This may have enabled us to find a significant interaction between antidepressant use and buprenorphine discontinuation, while potential interactions between buprenorphine and other psychotropic drugs may have gone unnoticed. However, patients in the active treatment group generally used less psychotropic drugs compared with the placebo group and had a lower prevalence of antidepressant use (31.8%) than that expected from recent reports in people with dementia (~40%).<sup>36,37</sup> Thus, the observed interaction between antidepressants and buprenorphine is likely to be of clinical relevance. While we did not find significant interaction effects between other psychotropic drugs and active buprenorphine, this may be due to insufficient power rather than the absence of such effects.

As shown in two recent studies, the use of opioid analgesics in the oldest nursing home patients with dementia is increasing.<sup>7,9</sup> Age is associated with increased pain, frailty, and dementia. In patients with severe pain, or very frail patients, it may be difficult to achieve full analgesic effect as the type or dose of analgesics required may not be tolerated by the patient. Because patients with dementia have not been included in safety studies, the evidence base to ensure appropriate prescribing is lacking. In the DEP.PAIN.DEM trial, neither did we find a significant change in pain intensity in either of the buprenorphine or placebo TDS groups during follow-up, nor did we find a significant treatment effect on pain between these groups.<sup>39</sup> However, this may be due to insufficient sample size as the DEP.PAIN.DEM trial was not powered to assess the effect of buprenorphine on pain. Further studies should investigate the efficacy and tolerability of buprenorphine and other opioid analgesics for pain in nursing home patients with dementia and painful symptoms.

Use of opioids in people with dementia should be based on a careful risk–benefit evaluation, including regular assessments of pain and potential adverse effects, in combination with nonpharmacological strategies as appropriate.<sup>34</sup>

This study has limitations. The included patients had clinically significant depressive symptoms at baseline, but not all had pain. Therefore, our results may not be generalizable to patients who receive buprenorphine for pain. Prescribers may have had a lower threshold for discontinuation upon adverse events in this study, for instance, the risk–benefit consideration may have been shifted toward a greater awareness of adverse events as the treatment was prescribed off-label. The patients' level of vulnerability to adverse events, and the relative prevalence of different types of adverse events, may also be different in people with advanced dementia and severe pain as opposed to the current sample which consisted of people with advanced dementia and depression without severe pain. Similarly, the adverse effects of buprenorphine TDS may differ between subgroups of pain patients (neuropathic/nociceptive; acute/chronic pain). Since the focus of the DEP.PAIN.DEM trial was to investigate the efficacy of pain treatment on depression, we did not diagnose the type and duration of pain. Therefore, future studies should investigate the safety and efficacy of buprenorphine TDS in people with dementia and different types of pain. Patients who were prescribed buprenorphine rather than acetaminophen used more regular analgesics and/or had difficulty swallowing tablets. This means that we may have selected more frail/multimorbid patients to receive buprenorphine/placebo as opposed to acetaminophen/placebo in the DEP.PAIN.DEM trial. However, this prescribing strategy mirrors clinical practice with a stepwise increase from non-opioid to opioid analgesics and the choice of transdermal formulation for patients who cannot swallow tablets; therefore, our sample should be similar to nursing home patients with dementia who receive buprenorphine TDS. We included a mixture of opioid-naïve patients, patients who had previously discontinued or received sporadic as-needed treatment with an opioid, and patients who received ongoing buprenorphine treatment; this is likely to have affected the observed pattern of adverse events which is not representative of an opioid-naïve population. Despite randomization, we found that patients who received active treatment used significantly less psychotropic and anticholinergic drugs, and fewer used antidepressants. This could potentially influence the results, as these drugs are associated with adverse outcomes in people with dementia.<sup>38</sup> However, because these drugs were more prevalent in the control group, the high occurrence of

adverse events in the active treatment group is likely caused by buprenorphine. We have not controlled for changes in concomitant drug use during study treatment. Physicians were instructed to avoid changes, particularly to psychotropic and analgesic drugs, but drug changes were not assessed in the 17 patients who discontinued treatment before week 6 assessment. The DEP.PAIN.DEM trial was designed with 90% power to detect a 2-point difference in depression (CSDD) from baseline to 13-week follow-up between active treatment (acetaminophen or buprenorphine) and placebo.<sup>39</sup> For the secondary outcomes reported in the present study, no a priori power analyses have been conducted. This is an important limitation, and the findings from the current analyses should therefore be interpreted with caution, in particular for the subgroup analyses with lower sample sizes. Because the estimated effect sizes have very wide CIs, the exact magnitude of increased risk remains uncertain. However, we have identified significant between-group differences in reported adverse events and discontinuation risk. Although adverse events were assessed by proxy, and are therefore likely to be affected by observer bias, the placebo-controlled design provides strong evidence that the difference in adverse events is caused by the active drug rather than observer bias. Therefore, we find it important to share the presented results. Further studies are needed to provide evidence of the safety and efficacy of transdermal buprenorphine for different types of pain in people with dementia.

## Conclusion

Buprenorphine appears to be poorly tolerated in people with dementia, with a higher prevalence of psychiatric adverse events compared with previous studies in cognitively intact elderly patients. Initiation of buprenorphine therapy is associated with reduced daytime activity. Although no dose adjustment is recommended for buprenorphine in elderly patients, our data suggest that people with dementia are susceptible to adverse events even at the lowest initial dose. When buprenorphine is administered to people with dementia, the patients' general condition pre- and posttreatment should therefore be monitored carefully, including assessments of intended and adverse treatment effects, particularly in patients using antidepressants.

## Acknowledgments

We wish to thank the patients, their relatives, and the nursing home staff for their willingness and motivation that made this work possible. The DEP.PAIN.DEM trial and AE and EF received grants from the Research Council of Norway.

BSH would like to thank the G.C. Rieber Foundation and the Norwegian Government for supporting our work at the Centre for Elderly and Nursing Home Medicine, University of Bergen, Norway. DA is a Royal Society Wolfson Research Merit Award Holder and would like to thank the Wolfson Foundation and the Royal Society for their support. Parts of the work by DDS were carried out at the Biostatistics and Data analysis core facility (BIOS), University of Bergen. This work was funded by the Research Council of Norway (sponsor's protocol code 221951) and has received a grant from the University of Bergen. The funders played no role in the design of the study; the collection, analysis, and interpretation of the data; writing of the report; and the decision to submit the article for publication.

This paper represents independent research [part] funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

## Author contributions

BSH, DA, and CB contributed in the conception of the study and in obtaining funding. All authors contributed to the study design, in carrying out the study, and in writing the manuscript. DDS, AE, EF, and BSH contributed to the statistical analysis. BSH and AE are guarantors for the study. All authors have approved the final article.

## Disclosure

Although Mundipharma Research Limited has supplied study medication, the company has had no influence on study design, data collection, analyses and interpretation of data, or final publications. The authors report no conflicts of interest in this work.

## References

1. Helvik AS, Engedal K, Benth JS, Selbaek G. Prevalence and severity of dementia in nursing home residents. *Dement Geriatr Cogn Disord*. 2015;40:166–177.
2. Zwakhalen SM, Koopmans RT, Geels PJ, Berger MP, Hamers JP. The prevalence of pain in nursing home residents with dementia measured using an observational pain scale. *Eur J Pain*. 2009;13:89–93.
3. Hadjistavropoulos T, Herr K, Prkachin KM, et al. Pain assessment in elderly adults with dementia. *Lancet Neurol*. 2014;13:1216–1227.
4. Reynolds KS, Hanson LC, DeVellis RF, Henderson M, Steinhilber KE. Disparities in pain management between cognitively intact and cognitively impaired nursing home residents. *J Pain Symptom Manage*. 2008; 35:388–396.
5. Achterberg WP, Pieper MJ, van Dalen-Kok AH, et al. Pain management in patients with dementia. *Clin Interv Aging*. 2013;8:1471–1482.



6. Tan EC, Jokanovic N, Koponen MP, Thomas D, Hilmer SN, Bell JS. Prevalence of analgesic use and pain in people with and without dementia or cognitive impairment in aged care facilities: a systematic review and meta-analysis. *Curr Clin Pharmacol*. 2015;10:194–203.
7. Jensen-Dahm C, Gasse C, Astrup A, Mortensen PB, Waldemar G. Frequent use of opioids in patients with dementia and nursing home residents: a study of the entire elderly population of Denmark. *Alzheimers Dement*. 2015;11:691–699.
8. Bauer U, Pitzer S, Schreier MM, Osterbrink J, Alzner R, Iglseder B. Pain treatment for nursing home residents differs according to cognitive state – a cross-sectional study. *BMC Geriatr*. 2016;16:124.
9. Sandvik R, Selbaek G, Kirkevold O, Aarsland D, Husebo BS. Analgesic prescribing patterns in Norwegian nursing homes from 2000 to 2011: trend analyses of four data samples. *Age Ageing*. 2016;45:54–60.
10. Tan EC, Visvanathan R, Hilmer SN, et al. Analgesic use and pain in residents with and without dementia in aged care facilities: a cross-sectional study. *Australas J Ageing*. 2016;35:180–187.
11. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8:287–313.
12. Pergolizzi J, Aloisi AM, Dahan A, et al. Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract*. 2010;10:428–450.
13. Vadivelu N, Hines RL. Management of chronic pain in the elderly: focus on transdermal buprenorphine. *Clin Interv Aging*. 2008;3:421–430.
14. Gallagher AM, Leighton-Scott J, van Staa TP. Utilization characteristics and treatment persistence in patients prescribed low-dose buprenorphine patches in primary care in the United Kingdom: a retrospective cohort study. *Clin Ther*. 2009;31:1707–1715.
15. Plosker GL. Buprenorphine 5, 10 and 20 µg/h transdermal patch: a review of its use in the management of chronic non-malignant pain. *Drugs*. 2011;71:2491–2509.
16. van Ojik AL, Jansen PA, Brouwers JR, van Roon EN. Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids. *Drugs Aging*. 2012;29:615–625.
17. Erdal A, Flo E, Selbaek G, et al. Associations between pain and depression in nursing home patients at different stages of dementia. *J Affect Disord*. 2017;218:8–14.
18. Farina N, Morrell L, Banerjee S. What is the therapeutic value of antidepressants in dementia? A narrative review. *Int J Geriatr Psychiatry*. 2017;32:32–49.
19. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Ageing Health*. 2008;4:311–320.
20. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr*. 2015;15:31.
21. Van Remoortel H, Raste Y, Louvaris Z, et al; PROactive consortium. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS One*. 2012;7:e39198.
22. Lambiase MJ, Gabriel KP, Chang YF, Kuller LH, Matthews KA. Utility of actiwatch sleep monitor to assess waking movement behavior in older women. *Med Sci Sports Exerc*. 2014;46:2301–2307.
23. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
24. Pernecky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry*. 2006;14:139–144.
25. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. *Eur J Pain*. 2014;18:1419–1430.
26. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. *Biol Psychiatry*. 1988;23:271–284.
27. Pergolizzi JV, Raffa RB, Marcum Z, Colucci S, Ripa SR. Safety of buprenorphine transdermal system in the management of pain in older adults. *Postgrad Med*. 2017;129:92–101.
28. Pautex S, Michon A, Guedira M, et al. Pain in severe dementia: self-assessment or observational scales? *J Am Geriatr Soc*. 2006;54:1040–1045.
29. Al-Tawil N, Odar-Cederlof I, Berggren AC, Johnson HE, Persson J. Pharmacokinetics of transdermal buprenorphine patch in the elderly. *Eur J Clin Pharmacol*. 2013;69:143–149.
30. Likar R, Vadla EM, Breschan C, Kager I, Korak-Leiter M, Ziervogel G. Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. *Clin J Pain*. 2008;24:536–543.
31. Gianni W, Madaio AR, Ceci M, et al. Transdermal buprenorphine for the treatment of chronic noncancer pain in the oldest old. *J Pain Symptom Manage*. 2011;41:707–714.
32. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain*. 2009;13:219–230.
33. Naples JG, Gellad WF, Hanlon JT. Managing pain in older adults: the role of opioid analgesics. *Clin Geriatr Med*. 2016;32:725–735.
34. McLachlan AJ, Bath S, Naganathan V, et al. Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. *Br J Clin Pharmacol*. 2011;71:351–364.
35. Kapil RP, Cipriano A, Friedman K, et al. Once-weekly transdermal buprenorphine application results in sustained and consistent steady-state plasma levels. *J Pain Symptom Manage*. 2013;46:65–75.
36. Janus SI, van Manen JG, IJzerman MJ, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *Int Psychogeriatr*. 2016;28:1775–1790.
37. Gulla C, Selbaek G, Flo E, Kjome R, Kirkevold O, Husebo BS. Multi-psychotropic drug prescription and the association to neuropsychiatric symptoms in three Norwegian nursing home cohorts between 2004 and 2011. *BMC Geriatr*. 2016;16:115.
38. Johnell K, Bergman GJ, Fastbom J, Danielsson B, Borg N, Salmi P. Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults. *Int J Geriatr Psychiatry*. 2017;32:414–420.
39. Erdal A, Flo E, Aarsland D, et al. Efficacy and safety of analgesic treatment for depression in people with advanced dementia: randomised, multicentre, double-blind, placebo-controlled trial (DEP.PAIN.DEM). *Drugs Aging*. In Press 2018.

## Clinical Interventions in Aging

### Publish your work in this journal

Clinical Interventions in Aging is an international, peer-reviewed journal focusing on evidence-based reports on the value or lack thereof of treatments intended to prevent or delay the onset of maladaptive correlates of aging in human beings. This journal is indexed on PubMed Central, MedLine,

CAS, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <http://www.dovepress.com/clinical-interventions-in-aging-journal>





Graphic design: Communication Division, UIB / Print: Skjipes Kommunikasjon AS



[uib.no](http://uib.no)

ISBN: 978-82-308-3590-6