Behavioral and Psychological Symptoms of Dementia

The impact of medication reviews in multicomponent interventions and the consequences of the Covid-19 restrictions

Marie H. Gedde

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2023

UNIVERSITY OF BERGEN

Behavioral and Psychological Symptoms of Dementia

The impact of medication reviews in multicomponent interventions and the consequences of the Covid-19 restrictions

Marie H. Gedde

Thesis for the degree of Philosophiae Doctor (PhD)

at the University of Bergen

Date of defense: 16.02.2023

Year: 2023

Title: Behavioral and Psychological Symptoms of Dementia

Name: Marie H. Gedde

Print: Skipnes Kommunikasjon / University of Bergen

Scientific environment

The Centre for Elderly- and Nursing Home Medicine (SEFAS), Department of Global Public Health and Primary Care (IGS), University of Bergen (UiB), coordinated this research. The Research Council of Norway (RCN) granted my position at Haraldsplass Deaconess Hospital, Bergen. Other collaborators were the Norwegian Research Centre (NORCE), Western Norway University of Applied Sciences (HVL), and the Dignity Centre, Bergen.

Postdoctoral research fellow Line Iden Berge, PhD, SEFAS and senior consultant psychiatrist at NKS Olaviken Gerontopsychiatric Hospital was my main supervisor. Professor Bettina S. Husebø, PhD, leader of SEFAS and researcher at the Department of Nursing Home Medicine, Bergen Municipality, and Associate Professor Mala Naik, PhD, geriatrician, senior consultant at Haraldsplass Deaconess Hospital and Department of Clinical Science, UiB, were my co-supervisors.

I attended PhD courses at UiB and the University of Oslo. I was also a member of the Research School of IGS, UiB, and the Norwegian PhD School of Pharmacy. The Pandemic Centre, IGS, UiB, widened my network. I also enjoyed being part of the Bergen Geriatric Research Group, the Network of Northern European Researchers in Deprescribing (NERD), and the European COST Network to Advance Best Practice and technoLogy on medication adherencE (ENABLE) CA1932.

Acknowledgements

Words cannot express my gratitude to postdoctoral research fellow Line Iden Berge for her wit, engagement, and constant support. I would like to express my most profound appreciation to Professor Bettina S. Husebø for her dedication to and ambitions for her PhD candidates. I would also like to extend my gratitude to Associate Professor Mala Naik for safeguarding this thesis' clinical relevance. I am grateful to Associate Professor Reidun Kjome for her engagement in social pharmacy and Professor Geir Selbæk for generously sharing his expertise in dementia research with me. I am also indebted to Assistant Professor Ipsit V. Vahia for providing international perspectives before and during Covid-19, and to Senior Engineer Janne Mannseth for supervising the analyses. RCN made this work possible.

I am grateful for the collegium at Haraldsplass Deaconess Hospital and UiB. I wish to thank the entire multidisciplinary group affiliated with LIVE@Home.Path, including collaborators in dementia care and research, yet the other PhD candidates deserve special credit: Thank you, Maarja Vislapuu, for your dedication and moral obligation towards colleagues, patients, and collaborators. Thank you, Eirin Hillestad, for being so enthusiastic and thorough. This has been a lot of work and a great deal of fun!

Thank you, Hanne Sether Lilleberg, for extending our friendship to include research. Thank you, Hilde Erdal, for discussions at the desk, on horseback, and in saunas. I am much obliged to you and your family. Also, the Sollien Ripmans generously provided me with a family in Bergen. To all my friends: I am happy that you are still there.

I would be remiss in not mentioning my family. Thank you for believing in me and allowing me to work from your homes while vagabonding. The down-to-earth presence of my brothers reminds me of what really matters to me. I must express my profound gratitude to my parents for their continuous encouragement. Falling in love has been a pleasant recreation in finalizing this thesis. Thank you, Erik, for watching the news and being ever so patient with me.

Marie, Bolstad, September 2022

Introduction

My grandfather, with whom I had a close relationship, received ambulatory homecare and later nursing home care as he gradually became more impaired by Parkinson's disease. I found this neurodegenerative disorder to elegantly illustrate the direct connection between drugs acting upon the central nervous system and related symptoms, as dopamine replacement therapy alleviates the hallmark motor symptoms (parkinsonism: slow movement, tremors, and rigidity), whereas overly high dopamine levels result in reduced impulse control and hallucinations.

During medical school, indications for drug therapy were emphasized, and excessive use of drugs was problematized. I became further aware of the widespread use of psychotropic drugs when working in the field of drug rehabilitation and in ambulatory homecare, for which the majority of patients were older adults. The clinical challenges in differentiating symptoms of neurodegenerative processes leading to dementia and substance abuse, as well as the side effects from psychotropic drugs, sparked my interest in the use of these drugs to manage behavioral and psychological symptoms in people with dementia; particularly in the process of deprescribing.

Limiting the use of psychotropic drugs also engages the attention of stakeholders and policymakers [1-6]. At the time of writing, the proposed new act on forced medication in Norway is controversial. If this bill is passed, a psychiatrist will be obliged to act as a consultee for general practitioners and nursing home physicians to prescribe coerced treatment with antipsychotic drugs for people with dementia [7].

The Covid-19 pandemic highlighted the direct effects of policy imperatives on dementia care. Concerns arose about a disproportionate impact on the mental health of older people with dementia in community settings and nursing homes [8-10]. I came to think of my grandfather, who did not live to endure these restrictions.

Contents

List of abbreviations

ADL	Activities of daily living
ATC	Anatomical Therapeutic Chemical Index
BPSD	Behavioral and psychological symptoms of dementia
CMAI	Cohen-Mansfield Agitation Inventory
COSMOS	COmmunication, Systematic pain management, Medication review, Organization of activities, Safety
Covid-19	Coronavirus SARS CoV-2 disease, 2019
(c)RCT	(Cluster-)randomized controlled trial
CSDD	Cornell Scale for Depression in Dementia
DPIA	Data Protection Impact Assessment
FAST	Functional Assessment Staging
FORTA	Fit FOr The Aged List
GDPR	General Data Protection Regulation
GP	General Practitioner(s)
ICD-10	International Classification of Diseases, 10-th version
ICPC	International Classification of Primary Care
IGS	Department of Global Public Health and Primary Care
LIVE	Learning, Innovation, Volunteers, Empowerment
MMSE	Mini-Mental Status Evaluation
NORGEP	Norwegian General Practice criteria
NPI (-NH/12)	Neuropsychiatric Inventory (-Nursing Home/12-domain version)
PAN.DEM	PANdemic in DEMentia study
PIM	Potentially innaproperiate medication
PwD	People with dementia
RCN	Research Council of Norway
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SEFAS	Centre for Elderly- and Nursing Home Medicine
UiB	University of Bergen
WHO	World Health Organization

Summary

Background: Behavioral and psychological symptoms of dementia (BPSD) are prevalent, often challenging to treat, and associated with earlier functional decline and admission to nursing homes. There is a need for evidence-based strategies to improve BPSD management in different care settings.

Aim: To prospectively investigate the impact of medication reviews in multicomponent interventions and the impact of the Covid-19 restrictions on BPSD.

Materials and methods: BPSD were assessed by the Neuropsychiatric Inventory and Cornell Scale for Depression in Dementia in two trials in Norwegian municipal dementia care. Psychotropic drug use (antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, and antidementia drugs) was evaluated in medication reviews. Medication reviews were conducted in nursing homes using collegial mentoring and systematic clinical evaluation in COSMOS, a four-month multicenter, multicomponent cluster-randomized controlled trial (2014-2015). General practitioners conducted medication reviews for home-dwelling people with dementia in LIVE@Home.Path, a stepped-wedge, closed-cohort, multicomponent cluster-randomized controlled trial (2019-2021). PAN.DEM was a prospective cohort study comparing BPSD in home-dwelling people with dementia before and during the Covid-19 restrictions when 'non-essential' healthcare services were withdrawn (2020).

Results: We found that BPSD deteriorated for home-dwelling people with dementia during the initial Covid-19 restrictions, while BPSD were not impacted by medication reviews in the multicomponent intervention conducted in nursing homes and general practice. The greatest reductions in psychotropic drugs were found among those who received several at baseline, and nursing home patients were prescribed psychotropic drugs more widely than home-dwelling people.

Conclusions and consequences: As BPSD were impacted by the withdrawal of 'care as usual' and not by medication reviews as part of add-on multicomponent interventions, this thesis highlights the importance of established services in dementia care for managing BPSD.

Sammendrag

Bakgrunn: Adferdsmessige og psykologiske symptomer ved demens (APSD) er vanlige, kan være krevende å behandle og er forbundet med raskere sykdomsprogresjon og tidligere innleggelse i sykehjem. Det er behov for mer kunnskap om behandling og håndtering av APSD i ulike deler av helsetjenesten.

Formål: Å undersøke om APSD blir påvirket av medikamentgjennomgang som ledd i multikomponente intervensjoner og Covid-19-restriksjonene.

Materiale og metoder: APSD ble undersøkt ved hjelp av Nevropsykiatrisk Intervjuguide og Cornell Skala for Depresjon ved Demens i to studier i norsk kommunehelsetjeneste. Foreskrivning av psykofarmaka (antipsykotika, anxiolytika, sedativa og hypnotika, antidepressiva og legemidler mot demens) ble evaluert ved legemiddelgjennomgang. Med kollegial støtte gjennomførte sykehjemsleger standardiserte medikamentgjennomganger i KOSMOS, en klyngerandomisert studie a fire måneders varighet utført i 33 sykehjem (2014-2015). Fastleger gjennomførte medikamentgjennomgang for sine hjemmeboende pasienter med demens i LIVE@Home.Path, en klyngerandomisert studie med stegvis implementering av en multikomponent intervensjon a seks måneders varighet i tre kommuner (2019-2021). I PAN.DEM ble APSD sammenlignet før og under Covid-19-restriksjonene i 2020, da omfattende smittevernstiltak ble iverksatt for å bekjempe koronavirusutbruddet.

Resultater: APSD ble forverret blant hjemmeboende personer med demens da de ikke fikk omsorg og tjenester som vanlig i Covid-19-pandemiens første fase. APSD ble ikke påvirket av medikamentgjennomgang i de multikomponente intervensjonene i sykehjem og allmennpraksis sammenlignet med kontrollgruppene som mottok vanlig omsorg. Størst reduksjon i bruk av psykofarmaka ble funnet blant dem som ved studiestart brukte flere medikamenter. Sykehjemspasienter brukte psykofarmaka oftere enn hjemmeboende personer med demens.

Konklusjon: Denne avhandlingen viser at ordinære tjenester i kommunal demensomsorg er viktig ettersom personer med demens opplevde symptomforverring under Covid-19-restriksjonene, mens medikamentgjennomgang som del av multikomponente intervensjoner ikke påvirket APSD.

List of Papers

Paper I Gedde MH, Husebo BS, Mannseth J, Kjome RLS, Naik M, Berge LI: Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial. Am J Geriatr Psychiatry 2021;29(3):304-315.

Paper II Gedde MH, Husebo BS, Mannseth J, Naik M, Selbaek G, Vislapuu M, Berge LI: The impact of medication reviews by general practitioners on psychotropic drug use and behavioral and psychological symptoms in home-dwelling people with dementia: Results from the multicomponent cluster-randomized controlled LIVE@Home.Path trial. BMC Med 2022;20:186.

Paper III Gedde MH, Husebo B, Vahia IV, Mannseth J, Vislapuu M, Naik M, Berge LI: The impact of Covid-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: a prospective cohort study (PAN.DEM). BMJ Open 2022;12:e050628.

Other publications not included in this thesis:

Gedde MH**,** Husebo BS, Erdal A, Puaschitz NG, Vislapuu M, Angeles RC, Berge LI: Access to and interest in assistive technology for home-dwelling people with dementia during the Covid-19 pandemic (PAN.DEM). Int Rev Psych 2021;33(4):404-411.

Berge LI, Gedde MH, Vidal JCT, Husebo BS, Hynninen KMJ, Knardal SE, Madsø KG: The acceptability, adoption, and feasibility of a music application developed using participatory design for home-dwelling persons with dementia and their

caregivers: The “Alight” app in the LIVE@Home.Path trial. Front Psychiatry 2022;13:949393.

Berge LI, Gedde MH, Husebo BS, Kjellstadli C, Vahia V**:** Age and Emotional Distress during Covid-19: Findings from Two Waves of the Norwegian Citizen Panel. Int J Environ Res Public Health 2021;18(18):9568.

Angeles RC, Berge LI, Gedde MH**,** Vislapuu M, Kjerstad E, Husebo BS: What factors increase informal care hours and societal costs in dementia care? A systematic review of Resource Utilization in Dementia (RUD) studies. Health Econ Rev 2021;11(1):37.

Vislapuu M, Angeles RC, Berge LI, Kjerstad E, Gedde MH**,** Husebo BS: The consequences of Covid-19 lockdown for formal and informal resource utilization among home-dwelling people with dementia: Results from the prospective PAN.DEM study. BMC Health Serv Res 2021;21:1003.

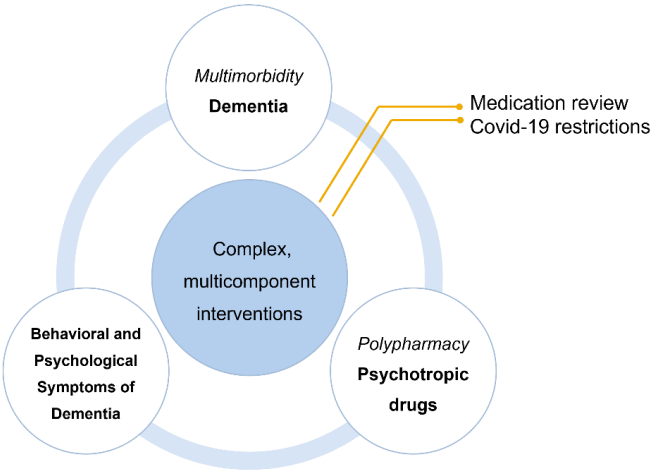
Puaschitz NG, Jacobsen FF, Mannseth J, Angeles RC, Berge LI, Gedde MH, Husebo BS: Factors associated with access to assistive technology and telecare in home-dwelling people with dementia: baseline data from the LIVE@Home.Path trial. BMC Med Inform Decis Mak 2021;21:264.

Husebo BS, Allore H, Achterberg W, Angeles RC, Ballard C, Bruvik FK, Fæø SE, Gedde MH, Hillestad E, Jacobsen FF, Kirkevold Ø, Kjerstad E, Kjome RLS, Mannseth J, Naik M, Nouchi R, Puaschitz NG, Samdal R, Tranvåg O, Tzoulis C, Vahia IV, Vislapuu M, Berge LI: LIVE@Home.Path — innovating the clinical pathway for home-dwelling people with dementia and their caregivers: study protocol for a mixed-method, stepped-wedge, randomized controlled trial. Trials 2020:21:510.

1. Background

Globally, people live longer lives [11], and with advancing age, both the incidence and prevalence of dementia increase [12, 13]. Dementia is a syndrome characterized by cognitive deterioration (see 1.1). Approximately 90% of people with dementia (PwD) experience behavioral and psychological symptoms (BPSD) such as depression, agitation, and psychosis (see 1.2) [14, 15]. Psychotropic drugs are often prescribed to manage BPSD (see 1.3). Due to multiple morbidities (multimorbidity), PwD are exposed to several drugs, also including psychotropic drugs, which increases the potential for compromised prescription safety (see 1.4). Several strategies have been introduced to improve prescribing practices since PwD might find it particularly difficult to engage with health services. Complex, multicomponent strategies to review medications may be helpful in dementia care, with integrations of services for somatic and mental health needs, while also meeting the social needs of PwD (see 1.5) The Covid-19 pandemic and the accompanying restrictions placed a significant strain on health care systems and communities (see 1.6). This thesis demonstrates the complex interplay between the health care services providing dementia care, focusing on BPSD management in both a pre-pandemic and pandemic context.

Figure 1.1 Thesis in context



Long-term care for older people in Norway

In Norway, long-term care is the responsibility of the welfare state, delegated to the municipalities [16]. The Norwegian Government emphasizes the municipalities' role – and potential – in enabling people to remain in their own homes longer and reducing the need for more costly institutional care [17]. Table 9.1, p. 107, outlines terms central to understanding variations in residency and formal care in Norway. Ambulatory homecare, day care, and nursing home care are mandatory primary health care services in all municipalities [18]. The term 'home-dwelling' constitutes people who live in ordinary or assisted housing, distinct from those receiving institutional care in nursing homes [16, 19, 20].

1.1 Dementia

1.1.1 The definition of dementia

Dementia is a syndrome characterized by deterioration in cognitive function caused by diseases and injuries affecting the brain to such an extent that this compromises independence in daily living [21]. In Norway, the International Classification of Primary Care (ICPC-2) is used for diagnostics in primary care, while the International Classification of Diseases, 10-th revision (ICD-10), is used in secondary care (Text box 1.1) [22, 23]. Regardless of the criteria used, both requires a syndrome duration of at least six months [24].

Text box 1.1 Dementia diagnosis by ICD-10

> *"Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation."*

1.1.2 The diagnostics of dementia

Most diagnostic evaluations for dementia in Norway are conducted by physicians in primary care, essentially regular general practitioners (GP) [25]. The national

guidelines on dementia outline the practical considerations for the diagnostic process, as summarized in Text box 1.2 [24, 25].

Text box 1.2 Basic diagnostic evaluation

The diagnostic workup should, as a minimum, include 1) a thorough medical history from the individual and third party (i.e., informal and formal caregivers); 2) an assessment that includes cognition including consciousness, level of functioning, BPSD (e.g, symptoms of psychosis, depression, anxiety, agitation), safety at home including the situation of the informal caregiver(s); 3) a clinical examination; 4) assessment of whether drugs cause the symptoms; 5) blood tests (e.g., vitamin B12 and folate levels, electrolytes, thyroid function); and 6) diagnostic imaging of the brain (e.g., magnetic resonance imaging, computed tomography scan).

Each municipality is urged to provide the GPs with the services of an interdisciplinary team dedicated to the assessment and follow-up of people with (suspected) dementia ('Demensteam') [25]. In 2018, 90% of the Norwegian municipalities provided such services [26], and of these, 93% used recommended assessment tools (see 3.2 for examples) [26]. In nursing homes, the staff assist the physician in obtaining the relevant information from the patient and next-of-kin. However, referral to secondary health services for a diagnostic evaluation is recommended if the initial workup is inconclusive, the patient is under 65 years of age, from an ethnic or cultural minority, or the clinical presentation is atypical, or complicated by BPSD or comorbidity (e.g., disabilities such as Down's syndrome and psychiatric and somatic disorders complicating the clinical picture) [25].

Young onset dementia

Young onset dementia is a distinct presentation of dementia affecting people <65 years of age [21]. Approximately 2,100 of PwD are living with young onset dementia in Norway, constituting 2% of all dementia cases [13]. By comparing PwD under and over the age of 65, a nationwide cross-sectional study from New Zealand found differences in demography, physical function, health characteristics, psychosocial well-being, and use of healthcare and support services; partly explained by the presentation of BPSD at higher rates in younger PwD [27]. These differences should

be considered in clinical care and research, and as young-onset dementia affects a minority of PwD [13], this thesis will concentrate on PwD solely ≥65 years of age.

1.1.3 Dementia etiologies

The dementia syndrome can be caused by a range of medical conditions. Even though accurate diagnosis depends on postmortem neuropathological examination, clinicians are usually able to provide a possible etiology based on the clinical characteristics and core biomarkers (e.g., atrophy and signs of cerebrovascular disease on structural imaging, spinal fluid markers such as beta-amyloid, total tau and phosphorylated tau, and reduced dopamine uptake in basal ganglia demonstrated by dopamine transporter imaging) [12, 28]. However, the boundaries between different dementia etiologies are indistinct and different pathologies often co-exist. Moreover, the understanding of etiologies is gradually shifting [12]. For instance, limbic-predominant age-related TDP-43 encephalopathy has been introduced to describe a clinical Alzheimer-like syndrome in the oldest old, yet is not currently acknowledged as a valid clinical diagnosis [12]. Table 1.1 outlines the principal pathological and early-phase clinical characteristics in the most common established etiologies among PwD with onset late in life.

Several forms of dementia exist that are less prevalent than those listed in Table 1.1. In the fourth wave of the Trøndelag Health Study, a population-based sample of 9,930 older Norwegians, frontotemporal dementia constituted 2% of all dementia cases, while less than 0.3% had other specified etiologies encompassing alcohol-related dementia, progressive supranuclear palsy, and post-operative sequela [13]. It may be argued that the distribution between etiologies in this study should be interpreted with caution due to the high prevalence of unspecified dementia (17%) and low prevalence of mixed dementia (9%), possibly because the diagnostic procedure depended heavily on information provided by the next-of-kin, even though clinical experts diagnosed dementia using all relevant information available. In addition to study design, the prevalence of etiologies varies between studies depending on the population being studied [12, 13, 29-31].

Table 1.1 Pathological and clinical characteristics of common dementia etiologies

	Alzheimer's disease[1]	**Lewy body dementias**[1]	**Vascular dementia**	**Mixed dementia**
Prevalence[2]	57%	4%	10%	≥9%
Pathological characteristics	Atrophy of the cerebral cortex and certain subcortical regions (parietal and temporal lobe, particularly in the hippocampus) due to synaptic and neuronal loss associated with tau and amyloid neuropathology [32].	Misfolded α-synuclein in the cell soma and the neuronal cell processes of the cortex and basal ganglia associated with a depletion of the neurotransmitter dopamine [33] .	Neuronal damage caused by heterogenous cerebrovascular pathologies, such as stroke, cerebral small vessel diseases, intracerebral hemorrhage, and subarachnoid hemorrhage [34].	Evidence of more than one possible cause of dementia [35].
Clinical characteristics[3]	Amnestic syndrome (characterized by short-term memory impairment) accompanied by difficulties in decision making, executive function and anomic aphasia [32].	Parkinsonism (motor and movement symptoms of rigidity, weakness, and tremors) and progressive cognitive decline with variations in alertness and attention, visual hallucinations, and rapid eye movement sleep behavior disorder [33].	Dysexecutive syndrome with fluctuating emotional, motivational, and behavioral symptoms[4] [34].	The symptoms are highly dependent on the continuum of the neuropathological substrates.
Characteristic BPSD[3]	Apathy, depression.	Hallucinations, disinhibitions.	Apathy, depression, irritability, agitation, pseudobulbar affect.	Dependent on the neuropathology.

Table legends: Lewy body dementias constitutes Dementia with Lewy bodies and Parkinson's disease with dementia, clinically differentiated based on the order in which symptoms develop [33]. [1]Neurodegenerative dementias characterized by the progressive loss of structure or function of neurons. [2]Percentage of all dementia cases based on the national standardized estimates for the prevalence of dementia in Norway [13]. [3]Early phase as distinctive features are often blurred as the dementia syndrome progresses [15] . [4]Symptoms are highly dependent on the injury mechanism, severity, size, location, and the constitution of the intact neuronal tissue.

1.1.4 Severity of dementia

Dementia is one of the leading causes of disability and dependency worldwide [21]. The World Health Organization (WHO) classifies dementia in mild, moderate, and severe stages in relation to dependency [21]. In mild dementia, the cognitive functioning affects the PwD's capacity to cope with everyday activities, yet is often overlooked because the onset is gradual. On progression to moderate dementia, the PwD become increasingly reliant on caregivers as the symptoms materialize. This means that the ability to perform complicated tasks decreases and that the PwD can no longer live independently. During severe dementia, there is complete dependence on caregivers, which implies that most PwD will require continuous care. Notably, this division into stages is rough and reflects syndrome advancement [21]. The prevalence and severity of dementia increase with higher levels of care [36]. Although approximately 66% of all PwD reside at home in Norway [13], around 42% of all those receiving home care have dementia, while the corresponding number in nursing homes is 84% [13, 37, 38].

Several tools are developed to uniformize the classification of the different stages of dementia [39-45]. One example is the Functional Assessment Staging Test (FAST), which describes the level of functioning rather than quantifying cognitive decline, p. 46 [39]. Cognitive impairment is often assessed using screening instruments such as the Mini-Mental Status Examination (MMSE), p. 46 [40]. Knowledge of the severity of dementia is necessary for accurate medical evaluation and healthcare provision.

1.2 Behavioral and psychological symptoms of dementia

BPSD cover a range of symptoms occurring in the course of dementia, including disturbed perception, thought content, mood, or behavior [46]. This section places BPSD in a historical context and describes individual symptoms and their clinical overlap, how they are assessed, factors to consider when evaluating them, and the distinction compared to delirium.

1.2.1 The historical context

Used since the 13th century, the term dementia translates as ‘derangement, insanity, folly’ [47, 48]. As such, the prototypical, most prevalent dementia etiology is named after Dr. Alzheimer, who in 1907 described BPSD in his 51-year old patient Auguste D. [47, 49]. She presented with delusions of infidelity towards her husband, accompanied by strong feeling of jealousy and emotional distress. In some periods, she also thought people were out to kill her.

1.2.2 Symptoms and subsyndromes

Auguste D. illustrates that BPSD are distressing and often co-occur. A review found relatively consistent results for the aggregation of BPSD across studies [50]. In the most cited study, which included home-dwelling PwD referred to outpatient clinics due to cognitive deficits or BPSD regardless of etiology, three subsyndromes were identified: psychosis, hyperactive behavior, and mood [51]. This study regarded anxiety as a separate symptom since it co-occurred with both mood-like and psychosis-like symptoms [51]. Table 1.2 lists and exemplifies a range of individual BPSD and how they are clustered in subsyndromes.

Systematic reviews find that BPSD are highly frequent and relatively persistent in dementia [19, 52]. Apathy is the most common and consistent symptom, while the other BPSD vary in frequency, but are rarely reported for less than 10% of PwD (except for euphoria) [19, 52]. In a sample of 11,448 PwD from the Swedish BPSD registry, the most prevalent symptoms were agitation (62%), irritability (55%) and depression (48%) [31]. In the prospective DemWest cohort following 223 patients with a first-time all-cause mild dementia enrolled from general practice in Norway, the most common symptoms reported during five years after diagnosis were apathy (80%), depression (63%), appetite changes (63%), and aberrant motor behavior (60%) [15]. This study also found etiology-related differences in BPSD profile and course (Table 1.1) [15, 28]. Although the increase in overall severity was moderate and associated with cognitive decline [15], the differences between symptoms across etiologies tended to decrease with dementia progression [53]. Following the same cohort for 12 years, single episodes represented the most common course, followed

by a relapsing course, while a stable course was less common [53]. Similarly, 97% of PwD in nursing homes experienced clinically significant BPSD, but individual symptoms fluctuated during more than four years of follow-up [14]. Reports dedicated to the persistence, frequency, and severity of BPSD vary considerably due to differences in setting, sample, design, and classification of dementia [19, 52].

Table 1.2 BPSD: an overview

Symptoms	Examples of how symptoms may manifest	Subsyndrome
Delusions	False beliefs, e.g., that someone is trying to harm or steal from them	Psychosis
Hallucinations	Hearing, feeling, or seeing people or things that are not real	Psychosis
Agitation	Hitting, kicking, restlessness, screaming	Hyperactive behavior
Euphoria	Excessive happiness or excitedness	Hyperactive behavior
Disinhibition	Impulsiveness, saying or doing inappropriate things	Hyperactive behavior
Irritability	Impatience, easily made angry or sad	Hyperactive behavior
Aberrant motor behavior	Pacing, restlessness, performing the same activity repetitively, wandering	Hyperactive behavior
Anxiety	Physical manifestations such as shortness of breath, separation anxiety, excessive worry, excessive fear that something bad is going to happen	
Depression	Sadness, slowed movements, early morning awakenings, mood congruent delusions	Mood
Apathy	Less interest in participating in activities of daily living and other activities	Mood
Sleep disturbances	Frequent nighttime awakenings, early morning awakenings, excessive daytime napping	Mood
Appetite changes	Weight loss or weight gain, changes in food preferences	Mood

Table legends: Symptoms to suggest BPSD on the Neuropsychiatric Inventory according to Watt et al., including the subsyndromes reported by Aalten et al. [51, 54, 55].

1.2.3 Assessment and evaluation of BPSD

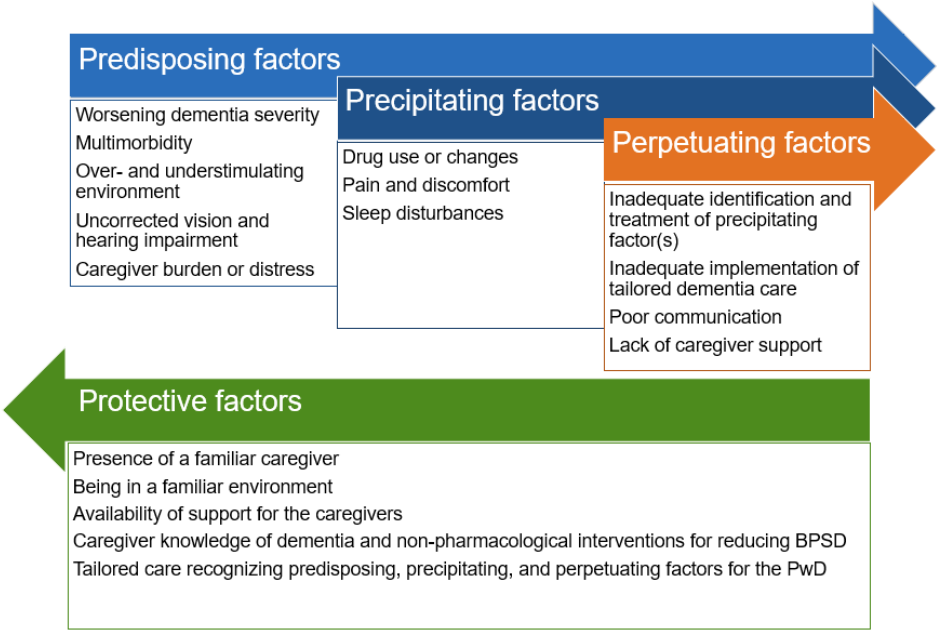
Many different tools to assess BPSD are utilized in clinical practice and research. The Neuropsychiatric Inventory (NPI) is an extensively used ‘broad spectrum’ assessment probing into several symptoms, p. 47, while the Cornell Scale for Depression in Dementia (CSDD), p. 47, and the Cohen-Mansfield Agitation Inventory (CMAI) are

examples of ‘narrow spectrum’ measures providing symptom-specific constructs [54, 56-58]. Current tools help identify and describe common BPSD, based on observations according to a proxy’s report (e.g., informal or formal caregiver) [58].

The neurobiology of the dementia syndrome does not fully explain BPSD presentation [12, 59-63], and there is general agreement that the contributors to BPSD are diverse and multifactorial and can be of a biological, psychological, and social nature [5, 12, 64]. The biopsycosocial model, for example, can be applied to describe how biological, psychological and social factors determine symptom manifestations, while the diathesis-stress model can be applied to explain how symptom trajectories depend on interactions between potential stressors, and the vulnerability of PwD to react to those stressors due to underlying neurobiological mechanisms [65, 66].

To evaluate BPSD, one should first carefully assess the acuity, that is characteristics of individual symptoms, when they occur, how often, and at what severity they present, and further their consequences, including safety issues. Secondly, one should consider the overall health status and look for causes in the PwD’s environment or situation, such as the examples of predisposing, precipitating, perpetuating, and protective factors listed in Figure 1.2, p. 22 [12, 55]. Notably, disparate symptoms co-occurring in the same PwD could have different triggers.

Figure 1.2 Factors to consider when evaluating BPSD according to Watt et al. [55]



Differential diagnosis: Delirium

Delirium is an important differential diagnosis to BPSD. This clinical syndrome is a direct physiological consequence of a medical condition or intoxication, and is characterized by abrupt onset and fluctuating disturbances in attention and awareness [67, 68]. The clinical picture often intersects with BPSD, but the typical hyperactive delirium often presents with psychotic symptomes and circadian dysregulation. A thorough medical evaluation is of upmost importance if delirium is suspected, and when the cause has been corrected the symptoms are generally expected to improve [69, 70]. PwD have a high suceptibility for developing delirium [68].

1.3 Managing BPSD

This section outlines general principles for BPSD management in primary care.

1.3.1 Nonpharmacological interventions

Nonpharmacological interventions are first-line treatments for BPSD [12, 25, 55, 64, 71]. A recent systematic review including 256 randomized controlled trials (RCTs)

found that multidisciplinary care, environmental modifications, social interactions, and reminiscence therapy are efficient in reducing depressive symptoms in PwD [72]. It should be noted that 41% of the 28,483 PwD included were home-dwellers or outpatients. These findings are in line with the conclusions of another recent systematic review of 189 RCTs controlled trials showing that such interventions also reduce aggression and agitation in PwD [73]. Here, approximately 18% of the 25,736 PwD were home-dwellers or outpatients. Similarly, the Norwegian national guidelines on dementia recommend environmental modifications, psychotherapy, and social interactions for PwD with depression of mild to moderate severity [25]. In clinical practice, nonpharmacological interventions addressing the factors listed in Figure 1.2 may be valuable in alleviating BPSD.

An international expert panel concluded that structured approaches using intervention manuals such as DICE (Describe, Investigate, Create, and Evaluate) [74] and TIME (Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms) [75] were the most promising non-pharmacological strategy for overall BPSD management and for agitation specifically [71]. Additionally, social prescribing programs linking PwD and caregivers with community initiatives provide new perspectives on holistic dementia care addressing their social needs [76].

1.3.2 Pharmacological interventions

BPSD may require psychotropic drugs when the PwD is in severe distress or endangers themselves or others [25, 55, 59, 77]. In these circumstances, nonpharmacological and pharmacological interventions should be combined. Moreover, management should be tailored according to the dementia etiology, severity, contributing factors (Figure 1.2), and local resources in the context of care [25, 55, 59]. The PwD and caregivers, as appropriate, should be involved in discussions relating to BPSD management including risk-benefit considerations and determination of therapeutic goals [55]. As PwD often have limited ability to report and evaluate treatment, the clinicians should select a follow-up time for re-evaluation

after a line of management is decided on, to ascertain effectiveness and minimize unnecessary, long-term psychotropic prescription [55].

Table 1.3 Psychotropic drugs used in managing BPSD

Classification[1]		Indications, examples	Substances, examples	Comments
N05A	Antipsychotic drugs	Symptoms of psychosis and aggression	Risperidone, aripiprazole, and olanzapine	Warning against the use of all types in PwD due to side effects (e.g., death, stroke, coronary heart disease, metabolic syndrome) [25]. Risk of serious sensitivity reactions with Lewy Body pathology [33].
N05B	Anxiolytic drugs	Short-term treatment of symptoms of anxiety	Oxazepam, diazepam, and hydroxyzine	
N05C	Hypnotic and sedative drugs	Insomnia	Zopiclone, zolpidem, and melatonin	
N06A	Antidepressant drugs	Symptoms of depression and anxiety, and neuropathic pain	Citalopram, sertraline, and mirtazapine	
N06D	Antidementia drugs	Slowing down disease progression	Donepezil, rivastigmine, galantamine, and memantine	Approved for PwD with Alzheimer's disease and Lewy body pathology [25].

Table legends: [1]According to the Anatomical Therapeutic Chemical Index [78].

The term BPSD covers a wide array of psychiatric symptomatology in a heterogenous population, which should be kept in mind when outlining general principles for pharmacological management (Table 1.3). The atypical antipsychotic agent risperidone is licensed for short-term treatment (<6 weeks) of psychotic symptoms and aggressive behaviors in Alzheimer's disease in Europe and Canada [25, 79]. Alternatively, Norwegian national guidelines on dementia recommend the use of aripiprazole and olanzapine for Alzheimer's disease and vascular dementia, even though these atypical antipsychotics are not licensed for treatment for psychosis and

aggression in PwD [25]. However, the effects of antipsychotics are modest in treating psychosis and agitation (including aggression), and the treatment comes with a risk of severe adverse effects (e.g., cerebrovascular incidents, extrapyramidal symptoms, and falls) and increased mortality in PwD [80, 81].

Antidepressants are proposed for the treatment of people with depression and dementia [25], and a meta-analysis suggested that serotonergic antidepressants are effective in managing overall BPSD, agitation, and depression [82]. The Norwegian national guideline on dementia proposes serotonergic antidepressants for the treatment of mood disturbances, as they have less anticholinergic activity than tricyclic antidepressants, which, in particular, are associated with a negative impact on cognition [25, 83]. Correspondingly, benzodiazepine receptor agonists (i.e., benzodiazepines and Z-drugs) are generally not well-tolerated in older adults due to side effects such as worsening gait, drowsiness, cognitive deterioration, and toxicities [84, 85]. Consequently, use by PwD should be avoided, if possible, and limited to brief stressful episodes of sleep disturbance in which agents with shorter half-life should be chosen, such as oxazepam. Non-benzodiazepine receptor agonist hypnotics such as melatonin could improve sleep due to a better safety profile yet current evidence shows somewhat mixed effects in PwD [25, 85].

Antidementia drugs (cholinesterase inhibitors and memantine) are approved for slowing down the progression of Alzheimer's disease, while the cholinesterase inhibitor rivastigmine is also indicated for Lewy body pathology [25]. Combination therapy with cholinesterase inhibitors and memantine has no additional benefits over monotherapy [25, 86]. While the evidence for their role in the treatment of BPSD is a matter of debate [59], a comparative safety and effectiveness study using data from 41 RCTs in a network meta-analysis concluded that neither anticholinesterase inhibitors nor memantine reduced BPSD [87]. Some cohort studies suggest that antidementia drugs may prevent the use of other psychotropic drugs. A cross-sectional survey from Japan found the use of antidementia drugs to reduce the risk of other psychotropic drug use among PwD when compared with non-users [88]. The

Norwegian national guideline on dementia provides no specific recommendation on the treatment of BPSD with antidementia drugs [25].

In clinical practice, these psychotropic drugs are widely prescribed for PwD [31, 38, 89-95]. In DemWest, 69% of the participants with early dementia and no previous psychiatric disorders took a least one psychotropic at the time of diagnosis (antipsychotics 8%, anxiolytics 10%, hypnotics/sedatives 10%, antidepressants 32%, and antidementia drugs 42%) [93]. The REDIC study followed 696 patients from admission to Norwegian nursing homes until death, of whom 80% had dementia [94]. On admission, 68% of the patients took ≥1 psychotropic drug (antipsychotics 14%, anxiolytics 17%, hypnotics/sedatives 22%, antidepressants 31%, and antidementia drugs 31%) [94]. Furthermore, the prescription rates increased during the first six months of stay, except for antidementia drugs [94].

1.4 Challenges with psychotropic prescribing practices

The heterogeneity of BPSD in terms of phenomenology, course, and cause challenges drug development and licensing [58, 61]. A reluctance to conduct trials on patients with poor prognosis, PwD among them, further adds to the challenge. Moreover, polypharmacy, defined as the concurrent use of multiple drugs (usually when patients take five or more regularly), increases the likelihood of adverse drug reactions and drug-drug interactions [96], yet PwD are at risk of both under- and overprescribing regardless of the number of drugs used [97, 98]. This issue is further complicated by pathophysiological changes affecting pharmacodynamics and pharmacokinetics, increasing their susceptibility to drugs with central nervous system effects [99]. As such, the number of drugs in use is of less interest. One should evaluate the quality of prescribing practices based on available evidence and considerations of individual patient factors and context [96].

Over the past decades, stakeholders and policymakers have stressed reduction in the use of psychotropic drugs, emphasizing antipsychotics, to improve medication safety in dementia care [2, 4, 5, 100], and in the same period, the use of antipsychotics has

decreased [5, 101-104]. A longitudinal retrospective study found that the UK National Dementia Strategy led to a decrease in antipsychotic prescriptions for 128,249 PwD in primary care from 2005 to 2015, although often replaced with other psychotropics such as benzodiazepines and antidepressants [103]. Compensatory upshifts in sedating psychotropics with less evidence of efficacy for BPSD are also reported in the US, following policy efforts and national campaigns to reduce antipsychotics in long-term dementia care from 2012 onwards, while there was no increase in the use of nonpharmacological interventions in the same period [5]. A high prevalence of multiple psychotropic drug use is found in PwD in various populations and is associated with severe BPSD, especially depression and anxiety, among nursing home patients [90, 105]. Studies conducted in Norwegian nursing homes between 1997 and 2009 showed a trend for increasing multi-use of psychotropic drugs [101], particularly for antidepressants in combination with sedatives and anxiolytics. Furthermore, psychotropic drugs have been found to threaten the quality of life of nursing home patients at all stages of dementia; the association grew stronger with the number of psychotropic drugs prescribed [106].

1.5 How to improve prescribing practices?

The appropriateness of prescribing can be assessed by explicit (criterion-based) and implicit (judgment-based) measures of both process and outcome [107]. Several process measures have been developed to detect potentially inappropriate medications (PIM) over the last 30 years [108]. Table 1.4 lists some frequently used process measures showing that most criteria are intended for older people, but not PwD in particular [109]. Explicit process measures generally alert the prescriber of PIM use and can be applied with little or no clinical judgment in distinct clinical settings, rather than taking co-morbidity or the patient's wishes into account, which is the strength of implicit process measures [107]. Implicit process measures allow the clinician to evaluate the patient's drug regimen individually, and, therefore, the reliability of findings in trials is more likely to be compromised compared to trials using explicit criteria [107]. The Medical Appropriateness Index is an example of an implicit yet standardized process rating that has been further developed to evaluate

the psychotropic drug prescriptions in PwD in nursing home research [110, 111]. Nonetheless, it is unclear whether inappropriate prescribing, defined by pharmacological process measures, is associated with important clinical outcomes (e.g., adverse outcomes and BPSD) [107, 108, 112, 113].

Table 1.4 Explicit criteria of the appropriateness of prescribing for older people

Author (year), country	**Tool**	**Criteria (n)**	**Intended for**	**Comment**
American Geriatric Society Expert Panel (2019), US [114]	Beers Criteria for Potentially Inappropriate Medication Use in Older Adults	Drugs or drug classes: n=30 Specific patient groups: n=16.	Older people, excluding those with a short expected lifetime.	First published in 1991, the 2015 and 2019 updates include PwD [114]; indicating that dextromethorphan/quinidine, antipsychotics, anticholinergics, benzodiazepines, and Z-hypnotics should be avoided for BPSD in PwD. NORGEP [115, 116] and PRISCUS [117] are examples of modified versions.
O'Mahoney (2015), Ireland and the UK [118]	Screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START) version 2 criteria	STOPP: n=80 START: n=30	Older people, excluding those with a short expected lifetime.	The STOPP criteria consider antipsychotic and tricyclic antidepressant prescriptions potentially inappropriate for BPSD.
Pazan (2016), Germany [119]	Fit fOR The Aged (FORTA) List	n=273 in 29 indications	Older people	Cross-therapeutic prioritization allowed. No recommendations for PwD specifically. Country- and region-specific adaptations [108].

Table legends: NORGEP: the Norwegian General Practice (-Nursing Home) criteria.

Medication reviews

Medication review is an approach to optimizing prescribing in clinical practice, which may include both implicit and explicit criteria for appropriateness. In addition to pharmacological appropriateness, the process can account for the perspectives of patient and prescribers [107]. The Pharmaceutical Care Network Europe defines medication reviews as: "*a structured evaluation of a patient's medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions*" [120].

The prescribing continuum spans therapy initiation, dose titration, changing or adding drugs, and switching or ceasing drug therapies. The term 'deprescribing' (Norwegian: 'avmedisinering') is increasingly used when the appropriateness of drugs is considered [121, 122]. Reeve et al. propose the following definition: "*Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes"* [121]. Scott et al. provide a more comprehensive definition: *"the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences"* [123]. Consequently, decisions about deprescribing of psychotropic drugs necessitate a review of the medications [124].

Norwegian GPs are instructed to conduct medication reviews for patients with polypharmacy and when deemed necessary [25, 125]. More specifically, they are strongly advised to evaluate the PwD's need for a medication review once or twice yearly based on such factors as cognition, BPSD, and activities of daily living (ADL) [25]. According to the regulations on medication management, a medication review is to be carried out upon admission to long-term nursing home care, and at least annually during residency [126]. Nevertheless, a retrospective observational study from Norway revealed that a medication review was not conducted for approximately 50% of routine care admissions in or after 2017, despite this being a statutory requirement for improving drug use, and that it took between one and twenty months

from admission until the first medication review [127]. The regulations do not specify the process other than that medication reviews should be conducted by physicians alone or in cooperation with others [126].

Gulla et al. developed an approach to systematic medication reviews for all drug classes prescribed for nursing home patients by collegial monitoring [128, 129]. The medication reviews were implemented as part of the multicomponent COSMOS RCT, which succeeded in improving the primary outcome quality of life in nursing home patients (2014-2015) [130]. The systematic medication review showed promising results for several secondary outcomes of COSMOS: antihypertensives were successfully deprescribed [131], daytime sleep was reduced [132], and there was improvement in communication, family and staff satisfaction and distress [133]. The majority (52%) of the included residents had severe dementia [130].

1.5.1 Psychotropic deprescribing through multicomponent interventions

Appropriate pharmacological interventions for PwD are a complex task [107, 134]. A qualitative systematic review showed that deprescribing of psychotropic drugs in PwD is often hindered by 1) the physicians not receiving the necessary information as the basis for evaluations and adjustments, 2) concerns about symptom relapse from reduction or discontinuations, both among PwD and their formal and informal caregivers, and 3) the physicians feeling insufficiently competent to make adjustments on their own [135]. These barriers could be overcome by interprofessional collaboration, communication, systematic procedures of assessment, and education [135]. An overview of reviews of qualitative and mixed-method studies of psychotropic prescribing for BPSD concludes that multicomponent interventions involving multiple stakeholders at various levels of the healthcare services may be effective in changing prescribing behaviors [134].

Complex, multicomponent interventions

Interventions with multiple interacting components are conventionally defined as complex [136, 137]. However, the UK Medical Research Council guidance provides

a broader and more detailed understanding of the concept; defining complexity on a continuum by the number of targeted organizational levels and variability in the target population, number and variability of outcomes, skills required by those delivering the intervention, and degree of flexibility or tailoring of the intervention, in addition to the components themselves [136]. Others define complex interventions by the ability of the intervention to take different forms in different contexts and non-linear causal pathways [138], or by recognizing the potential powers of the individual parts and the whole of the intervention [137]. Many interventions are equally open to either simple or complex forms of analysis as there are few (if any) truly simple interventions [138].

Multicomponent interventions constitute a subgroup of complex interventions and are defined as interventions with at least two components [139]. One could debate, however, what counts as a component [140]. Extending a systematic review of complex, multicomponent interventions, key informants suggested that a component should exert an independent influence on outcomes, and that implementation may not always involve all the components [140]. The issue of complexity may be downplayed or emphasized in analyses based on assumptions regarding the components' ability to cause changes in outcomes [137, 138].

Regarding PwD, there is little evidence to inform deprescribing of drugs in general [124]. In line with most antipsychotic deprescribing studies in PwD who are resident in nursing homes [141], the COSMOS intervention encompassed multiple components (COmmunication, Systematic pain management, Medication review, Organization of activities, Safety) to improve the primary outcome quality of life, and medication reviews were considered one of several components to achieve this [128] WHELD, for instance, demonstrated the utility value of best practice guidelines in reducing antipsychotics in PwD in real-life nursing home practice, yet the best clinical outcomes of medication reviews were found when implemented alongside non-pharmacological interventions [142]. Table 1.5 lists examples of original research investigating the impact of medication reviews conducted by physicians as part of multicomponent interventions on psychotropic drugs for BPSD.

Table 1.5 Medication reviews in multicomponent interventions on psychotropic drugs for BPSD

Author (year)	Study population; country (year)	Intervention: components	Key findings relating to 1) psychotropic drugs and 2) BPSD
Ballard (2016) [142]	277 nursing home patients with dementia; the UK (2011-2012).	WHELD: 1) Staff training in person-centered care alone or in combination with a) physician led clinical antipsychotic medication review, b) social intervention, or c) exercise.	**1)** Antipsychotic review reduced antipsychotic use by 50%. **2)** The group receiving antipsychotic review alone showed a worsening in BPSD compared to those receiving treatment as usual. This effect was mitigated by the concurrent social intervention.
Cossette (2020) [143]	464 nursing home patients with dementia and ≥1 antipsychotic prescription; Canada (2018).	OPUS-AP*: 1) Update and dissemination of the local clinical guidelines for antipsychotic deprescribing; 2) staff training component of patient-centered approaches to care.	**1)** 86% reduction in antipsychotic use[1]; reductions in the use of benzodiazepines, but not antidepressants. **2)** Reductions in psychotropic drugs use was associated with reduced agitation, but had no impact on psychotic symptoms.
Fossey (2006) [144]	346 patients residing in specialist nursing homes for people with dementia; the UK (2003-2004).	1) Psychiatrists conducted the revisions and extended their recommendations to the physicians of patients in both groups; 2) Training and support to staff in the intervention group.	**1)** 19% reduction in antipsychotic use[2]. **2)** No difference in agitation between the groups.
Mesquida (2019) [145]	240 nursing home patients with dementia prescribed psychotropic drugs ≥ 3 months; Spain (2012-2014).	*1) Development of therapeutic consensus guidelines for BPSD management; 2) Patient-centered multidiciplinary joint review.	**1)** 28% reductions in psychotropic drugs[3]. Highest reduction rate for antipsychotic drugs. **2)** BPSD were not evaluated.
Westbury (2018) [146]	12,157 nursing home patients[4]; Australia (2014-2016).	RedUSe*: 1) Staff education on psychotropic drugs and nonpharmacological strategies for managing BPSD; 2) multidiciplinary psychotropic review.	**1)** Reduction in antipsychotic and benzodiazepine drug use, with no increased use of antipsychotics, benzodiazepines, anxiolytics, hypnotics/sedatives, or antidepressants. **2)** No deterioration in BPSD.

Table legends: See 9.2 for details of the search strategy. [1]: Cessation or dose reduction. [2]: Number taking antipsychotics. [3]: Antiparkinson drugs, antiepileptic, benzodiazepines, hypnotics/sedatives, antidementia drugs, antipsychotics, and antidepressives. [4]: Dementia not specified, yet dementia diagnosis was recorded in 58% of another sample drawn from RedUSe [147]. *Prospective longitudinal intervention.

There is a paucity of robust evidence of the impact of deprescribing interventions on BPSD and other clinical outcomes [124, 148], particularly in home-dwelling PwD [124]. At the time of writing, feasibility studies and protocols underpin the interest in medication reviews in multicomponent interventions for PwD [149-153].

Implementing complex, multicomponent interventions

Even a superbly designed intervention will not exert any change if the process of implementation is futile, yet the process evaluation of implementation is often insufficiently reported in RCTs [154]. The study of methods and strategies that hinder or facilitate the uptake of evidence-based practice into regular use is referred to as implementation science [155]. Text box 1.3 outlines the taxonomy of implementation outcomes, i.e., effects of deliberate and purposive actions to implement an intervention [156]. Effectiveness-implementation trials evaluate the effectiveness of clinical interventions while also assessing their implementation [155, 157].

Text box 1.3 Taxonomy of implementation outcomes by Proctor et al. [156]

- Acceptability: The perception among implementation stakeholders that the intervention is agreeable, palatable, or satisfactory.
- Adoption: The intention, initial decision, or action to try or employ the intervention.
- Approperiateness: The perceived fit, relevance or compatibility of the intervention to address a particular issue or problem.
- Cost: The cost impact of the implementation effort.
- Feasibility: The extent to which the intervention can be successfully used or carried out within a given agency or setting.
- Fidelity: Adherence to the description of the intervention as intended in the protocol or as intended by the developers.
- Penetration: The reach or integration of a practice within a service setting and its subsystems, equivalent to ‘reach’ in a service systems.
- Sustainability: The extent to which the intervention is integrated into practice within a service setting.

1.6 The Covid-19 pandemic

The Covid-19 emergency forced countries all over the world to implement multiple restrictions to contain the epidemic (Text box 1.4). In Norway, an intervention encompassing multiple restrictive measures was implemented: 1) hygiene measures, 2) isolation of infected persons and 3) quarantine of their close contacts, 4) restrictions on movements, 5) reduced social contact within the population, and 6) comprehensive protective measures for high-risk groups such as visitation-bans for nursing home patients receiving integrated healthcare [158].

Text box 1.4 Covid-19

- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of zoonotic origins and causes coronavirus disease 2019 (Covid-19) [159].
- SARS-CoV-2 is mainly transmitted via the respiratory route when people inhale droplets and small airborne particles [160]. The risk of contracting the virus increases when people are in close physical proximity to each other [160].
- The World Health Organization declared Covid-19 a pandemic on March 11, 2020. In Norway, national Covid-19 restrictions were announced on March 12, 2020 [158, 161], aiming to reduce the spread of the virus by minimizing physical contact [162].
- The most common symptoms are fever, cough, fatigue, and loss of smell and taste. However, symptoms may vary in character and severity depending on interactions between the infected individuals, characteristics of the virus (e.g., genetic variations, viral load, and coinfection), and the environment [163]. A systematic review concluded that dementia was the main factor influencing mortality in older adults with Covid-19 [164].

Already during the roll-out in March 2020, the Word Health Organization expressed concerns that such comprehensive restrictions threatening the provision of usual care and limiting social interactions would exaggerate BPSD [8]. While the earliest publications on the impact of Covid-19 restrictions on PwD were broad and rather speculative [165], the vast majority of initial original publications utilized cross-sectional designs. Table 1.6 gives an overview of the longitudinal quantitative research on BPSD during Covid-19, showing a lack of prospective data on the effects of the pandemic restrictions on BPSD.

The pandemic posed fundamental challenges to the integrity of clinical dementia research. In our ongoing LIVE@Home.Path trial enrolling home-dwelling PwD, the Covid-19 restrictions forced us to halt the implementation of the multicomponent intervention [166]. We, therefore, pivoted our research towards the consequences of the restrictions, nesting a prospective cohort study within LIVE@Home.Path [167].

Table 1.6 Prospective cohort studies on BPSD during Covid-19

Authors (year)	**Country: time conducted**	**Study population**	**Key findings**
Giebel (2021) [168]	UK: the first three months of lockdown[1].	377 participants; either caregivers to PwD, older adults, or PwD (10%).	In PwD; no change in level of anxiety and depression. In the total sample; the prevalence of anxiety decreased and depression increased.
Lara (2020) [169]	Spain: before vs during lockdown[2].	40 home-dwellers older than 60 years (50% with mild Alzheimer's disease) and their informal caregivers.	Increase in BPSD overall, and specifically for levels of agitation, apathy and aberrant motor behavior.
Moretti (2021) [170]	Italy: during vs after lockdown[3].	221 home-dwelling people with vascular dementia and their informal caregivers.	Increase in BPSD overall during lockdown, and specifically for delusions, hallucinations, depresssion, anxiety, and apathy. Benzodiazepines and antipsychotics were prescribed more often during lockdown. BPSD and psychotropic drug use decreased slightly after lockdown.
Sizoo (2022) [171]	The Netherlands: during easing of restrictions[5].	252 PwD in 19 nursing homes.	Agitation and depression decreased. Psychotropic drug use remained stable throughout the first wave.
Vernuccio (2022) [172]	Italy: before vs after lockdown[4].	100 outpatients with mild cognitive impairment (28%) or dementia (72%).	Increase in BPSD overall, and specifically for agitation, wandering, and disinhibition in PwD.

Table legends: See 9.2 for details of the search strategy. [1]: During lockdown, April-May 2020, and two subsequent time points 6 and 12 weeks later, ending Aug 2020. [2:] Before lockdown, Feb-Mar 2020, vs during lockdown, April 2020. [3]: Start lockdown, Mar 2020, at the end of lockdown, May 2020, and after lockdown, July 2020. [4]: Before and after lockdown, between Jan 2019 and May 2021, median follow-up: 10 months. [5]: BPSD were assessed monthly as the restrictions were gradually lifted, May-Aug 2020, while psychotropic drug use (antipsychotics, antidepressants, benzodiazepines including use on-demand, and antidementia drugs) was retrieved from medical records monthly from before the lockdown onwards, Feb-Aug 2020.

1.7 Rationale for this thesis

As outlined, BPSD result from complex interactions between dementia etiology, severity, and environment which is a challenge for management in clinical practice. As such, we need evidence-based strategies to improve BPSD management in different care settings. This thesis, therefore, investigates if and how BPSD are impacted by medication reviews implemented in multicomponent nonpharmacological interventions, and whether the withdrawal of ‘non-essential’ health care services during Covid-19 lockdown impacted BPSD.

2. Aim of the thesis

The overarching aim of this thesis is to prospectively investigate the impact of medication reviews in multicomponent interventions and the impact of the Covid-19 restrictions on BPSD in PwD. The following objectives further define the aim:

I. To investigate the impact of medication reviews using collegial mentoring and systematic clinical evaluations as part of a multicomponent intervention on the number of psychotropic prescriptions, BPSD, and ADL in nursing home patients.
II. To investigate the impact of medication reviews as part of a multicomponent intervention on the number of psychotropic prescriptions and BPSD in home-dwelling PwD and to quantify change in patient-GP communication evaluated by their informal caregivers.
III. To investigate the impact of the Covid-19 restrictions on BPSD in home-dwelling PwD.

Initially, this thesis sought to investigate psychotropic drug use in home-dwelling PwD and whether medication reviews as part of an at-home and a nursing home multicomponent nonpharmacological intervention impacted BPSD. As the pandemic shifted the research process, we adopted the theme for one of the papers due to the actuality of the Covid-19 restrictions.

3. Materials and methods

3.1 Data sources

The three papers included in this thesis are substudies analyzing the secondary outcomes of two trials (Table 3.1). The development and conduct of these trials generated both quantitative and qualitative data. The perspective of this thesis does not concern components, systems, or processes but rather outcomes, taking into consideration that the multicomponent interventions aimed for effectiveness (performance under real-world conditions rather than ideal conditions) and the overarching aim of this thesis is to investigate their impact on BPSD in PwD [138].

Table 3.1 Outline of data sources for Paper I-III

	I: COSMOS	**II: LIVE@Home.Path**	**III: PAN.DEM**
Design (year)	Cluster randomized controlled trial (2014-2015)	Stepped-wedge, cluster randomized controlled trial (2019-2021)	Prospective cohort study nested within LIVE@Home.Path (2020)
Multicomponent intervention	COSMOS[1]	LIVE[2]	Covid-19 restrictions
Inclusion criteria	- >2 weeks of residency in a participating nursing home unit - ≥65 years old	- Dementia diagnosis - MMSE 15-26 or FAST 3-7 - Home-dwelling in Bergen, Bærum, and Kristiansand - ≥ 65 years old - Weekly contact with the informal caregiver	- Dyads not lost at 6 months follow-up in LIVE@Home.Path
Exclusion criteria	- Expected survival <6 months - Schizophrenia	- Expected survival <4 weeks - Participation in other trials	
Lost at follow-up	- Moved from the nursing home unit - Deceased - Withdrawal of consent	- Long-term nursing home care - Deceased - Withdrawal of consent	
N	- 723 nursing home patients	- 280 dyads of PwD and informal caregivers	- 126 dyads

Table legends: : [1]: Communication, Systematic pain management, Medication review, Organization of activities, Safety. [2]: Learning, Innovation, Volunteers, Empowerment emphasizing medication reviews.

3.1.1 The COSMOS trial

COSMOS was a 4-month multicenter, multicomponent, single-blinded cluster randomized and controlled effectiveness-implementation hybrid trial with follow-up at month nine. The five components (Table 3.1) synergistically aimed at improving nursing home residents' quality of life (trial's primary outcome).

Table 3.2 outlines key information regarding sponsors, approvals, and registration, while the process development and protocol are described elsewhere [128-130].

Table 3.2 The COSMOS trial

Design (year)	Sponsors	Approval	Registration
Cluster randomized controlled trial with internal pilot (2014-2015)	RCN 222113; Rebekka Ege Hegermanns' Foundation	REC West Norway 2013/1765	ClinicalTrials.gov: NCT02238652

Table legends: RCN: The Research Council of Norway Sponsor's Protocol Code; REC: Regional Committee for Medical and Health Research Ethics.

Setting and participants

The participants resided in 33 nursing homes constituting 67 units (one unit defined as one cluster). The nursing homes were located in the municipalities of Askøy, Bergen, Bærum, Fjell, Øygarden, Sarpsborg, Kvam, and Sund in Southern Norway, recruited to ensure a representative population. The managers of the nursing homes invited authorized participation before the units were allocated at random to the intervention or control group and the patients were recruited. Randomizaton was performed as a constrained complete list securing matched geographic and monetary status. From August 1, 2014 to March 15, 2015, 723 nursing home patients were enrolled. Table 3.1 lists patient inclusion and exclusion criteria. Participants were lost to follow-up if they were deceased or moved from the nursing home unit.

Intervention

Clusters of patients randomized to the interention group received the COSMOS intervention:

- **Co**mmunication: a systematic process of advanced care planning and regular communication between the patient, relatives, and staff embedded across the entire COSMOS program.
- **S**ystematic assessment and treatment of pain: evaluation of pain behavior utilizing the Mobilization-Observation-Behavior-Intensity-Dementia-2 pain scale [173].
- **M**edication reviews: conducted by the nursing home physician together with the staff and two researchers, who provided collegial mentoring [129]. The multidiciplinary team evaluated the necessity of the prescriptions for each patient based on the results of clinical assessments and an online database of drug interactions [174], p. 117. The START/STOPP 2 criteria, the Norwegian Medicines Agency's checklist for medication reviews, and a list of drugs with anticholinergic profiles further supported the decisions [118, 175, 176]. The nursing home physician was responsible for all medical treatment of the patient and made the final decisions. The relatives were informed by the staff after this decision meeting and encouraged to observe the patient and give feedback if any changes in the patient`s behavior were observed that might be related to a change in the drug regime.
- **O**rganization of activities: development of an individual plan for meaningful activities to improve the daytime activity provision for patients.
- **S**afety: embedded across the entire COSMOS program.

Implementation

The COSMOS intervention was implemented during a two-day seminar for nursing home staff, physicians, and nursing home managers. Following oral presentations by the researchers, the attendees participated in discussions and roleplay actualising ethical and practical considerations related to the COSMOS intervention. At least two nurses attended the seminar from each unit, making them ambassadors responsible for implementing COSMOS in their unit. They were provided with written material and patient logs to secure promotion and implementation. The ambassadors organized lunchtime meetings that were repeated several times weekly. For each week in a four-

week cycle during the four-month intervention period, one of the COSMOS components was in focus. The researchers provided telephone support to the ambassadors every other week during the intervention period. Additionally, a one-day midway seminar was organized to support the COSMOS ambassadors and standardize the implementation process.

While receiving integrated healthcare as usual, the *control group* were waiting to receive the intervention. After trial completion, the researchers introduced the staff at the control units to the COSMOS intervention.

Data collection

Patients were assessed at baseline and four- and nine-month follow-up. Researchers evaluated eligibility, and included patients in the trial. As several assessment tools require knowledge of the habitual state of the patient, nursing home staff who knew the patients well performed the assessments that were not blinded to allocation status.

Sample Paper I

Paper I includes all the controls and those patients in the intervention group receiving a medication review among participants not lost to follow-up at four months.

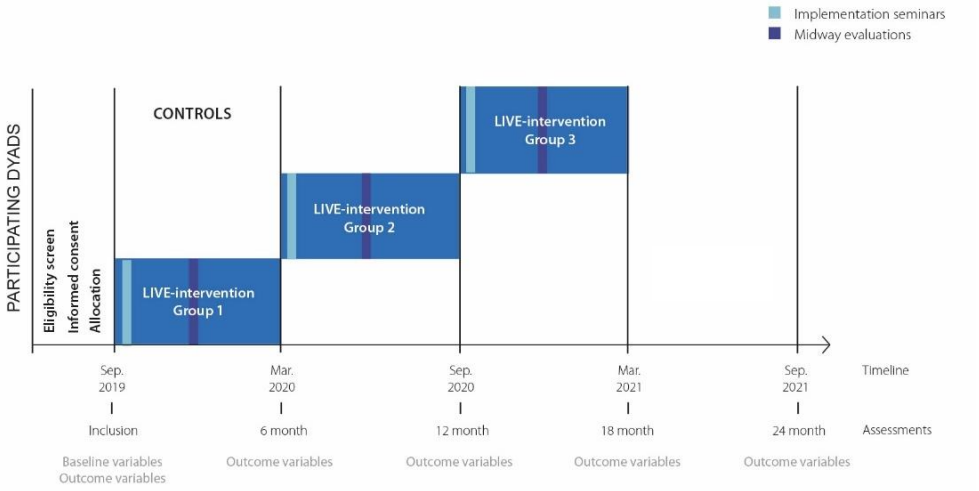
3.1.2 The LIVE@Home.Path trial

LIVE@Home.Path was a stepped-wedge, closed-cohort cluster randomized controlled hybrid trial aiming to implement and effect-evaluate a multicomponent intervention for dyads of home-dwelling PwD and their informal caregivers. The overall aim was to support the dyads allowing the PwD to live safer, longer, and more independently at home, with improvement in the primary outcomes cost-effectiveness and caregiver burden. The title of the trial communicates both the acronym of the four intervention components (Table 3.1) and the concept of innovating the clinical pathway for dementia treatment and care at home.

RCN (273581) and the Dignity Centre funded LIVE@Home.Path. It obtained ethical approval from the Regional Committee for Medical and Health Research Ethics

North Norway (2019/385) before we recruited participants. The development is outlined in Table 9.3, p. 120, on which the protocol provides further details [166].

Figure 3.1 The LIVE@Home.Path trial: Design, implementation, and assessments



Setting and participants

The feasibility study was conducted in Bergen from 2017 to 2019 [177], while LIVE@Home.Path was conducted in Bergen, Bærum, and Kristiansand (Norway). Recruitment of dyads was scheduled for May to September 2019, but extended to include November 2019 [166]. We screened 428 dyads consisting of a PwD and informal caregiver for participation, of whom 280 were included. Block-randomization was used to allocate the dyads to three groups receiving the intervention sequentially in periods of six months' duration. Each group included three clusters, one from each municipality. A pragmatic restrain was used to secure that each cluster included dyads from different municipal geographic areas. Table 3.1 lists dyad inclusion and exclusion criteria and reasons for loss to follow-up.

Intervention

The coordinators introduced the dyads to the LIVE components and tailored the intervention according to their needs:

- **L**earning: educational programs on dementia for the PwD and informal caregivers arranged by the healthcare services locally.

- **I**nnovation and Information and communications technology: information about relevant assistive technology and telecare available in the municipality [178, 179].
- **V**olunteer support: matching of PwD with volunteers from nonprofit organizations (e.g., the Red Cross and Norwegian Association of Public Health).
- **E**mpowerment: the continous process of communication in advanced care planning and medication reviews in collaboration with the GP. If welcomed by the dyads, the coordinators requested a medication review directly from the PwD's regular GP, p. 128, and provided a report with the results from clinical assessments, p. 129. The informal caregiver and coordinator were encouraged to join the PwD's GP consultation. The procedure for conducting the medication review was not standardized and the GP was responsible for the PwD's medical treatment.

Implementation

The coordinators were nurses, learning disability nurses and occupational therapists experienced in working with PwD in the local context. To enable the coordinators to tailor the intervention to each dyad's needs, they completed two-day seminars comprising lectures, role-plays, and discussions. Furthermore, pocket manuals describing core features of the intervention guided them in addressing the individual intervention components. The pocket manuals also included checklists to document the extent to which they had introduced the components. Additionally, a one-day midway seminar and telephone follow-ups every 14 days were organized for the coordinators allowing for discussion of obstacles and pitfalls to further standardizing and ensuring implementation (Figure 3.1) The GPs were informed of the dyads' participation in the trial when their patients were scheduled to receive the intervention, p. 128.

While waiting for the intervention (i.e., *controls* in Figure 3.1), the dyads received care as usual. While care for home-dwelling PwD is not standardized in Norway, it usually involves 0-36 hours/month of ambulatory homecare, 0-5 days/month of day

care, and medical follow-up provided by the regular GP (Table 9.1, p. 107) [36]. Some PwD also receive respite care at a nursing home occasionally or at fixed intervals, for instance of two to three weeks' duration every four to six weeks.

Data collection

Both the PwD and caregivers underwent a 60-90 minutes assessment every six months in the PwD's home (Figure 3.1). A one-day seminar prepared the data collectors (nurses, learning disability nurses, and occupational therapists) for collecting data blind to allocation status. During data collection, they were also supported with written material and supervision, as well as assistance. The data collectors used tablets to protect sensitive data and facilitate data management [180], as LIVE@Home.Path piloted software providing secure data collection, transfer to, and storage on, a secure server at UiB [181].

Sample Paper II

Paper II includes all dyads completing the first six-month period, which resulted in a 1:2 intervention-to-control ratio (Figure 3.1).

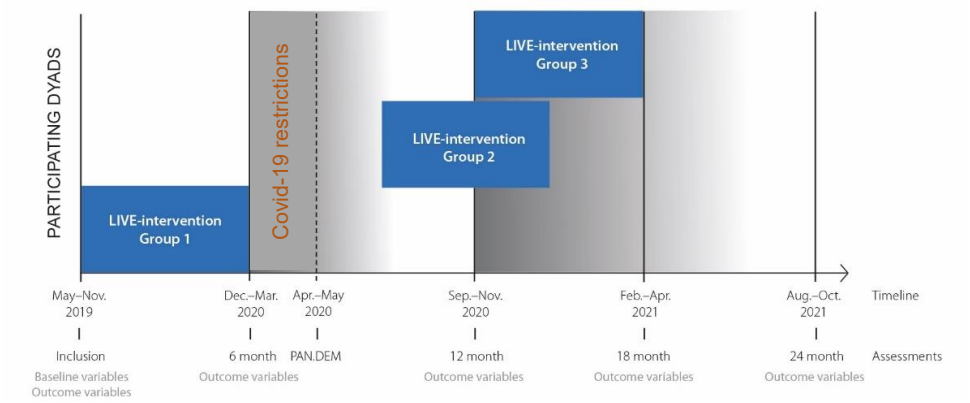
3.1.3 The PAN.DEM study

The PANdemic in DEMentia (PAN.DEM) study was launched to investigate whether and how home-dwelling people with dementia were affected by the Covid-19 restrictions. PAN.DEM is a prospective cohort study nested within LIVE@Home.Path, as the intervention protocol was halted in the pandemic scenario (Figure 3.2). The development and execution of PAN.DEM are described in detail elsewhere [167].

Intervention and implementation

The Covid-19 restrictions, p. 34, left 'non-essential' health care services withdrawn and consequently halted the LIVE@Home.Path trial protocol from March 12 to late spring 2020 [167].

Figure 3.2: The PAN.DEM study nested within the LIVE@Home.Path trial



Setting and participants

All dyads still in LIVE@Home.Path in March 2020 were eligible for inclusion in the PAN.DEM cohort. Following ethical approval on April 6, 2020, we consecutively invited caregivers from all three municipalities using non-systematic lists with their contact information. We considered the potential respondents unreachable after two calls and a text message. Recruitment lasted until the national Covid-19 restrictions were eased after nine weeks in mid-May 2020 [161], leaving a cohort of 126 dyads [167].

Data collection

The researchers conducted all the PAN.DEM telephone interviews lasting 20-40 minutes. Data was handled with respect for the approved procedures in LIVE@Home.Path. The PAN.DEM assessment included selected tools from previous assessments, in addition to pandemic-specific questions. An English version of the interview is available online [167].

Sample Paper III

Paper III includes dyads who completed the pre-pandemic six-month assessment before March 12, 2020, and the pandemic assessment between April 20 and May 15, 2020.

3.2 Assessment tools

The papers in this thesis are based on data from assessment tools used extensively in research and clinical settings concerning older people and PwD. Table 3.3 outlines the use of these tools in the trials, while the following paragraphs describe them in closer detail. Additionally, data on demographics, use of drugs, and information related to Covid-19 is utilized.

Table 3.3 The assessment tools and how they are used in Paper I-III

Assessment tools	I	II	III
Mini-Mental Status Evaluation (MMSE) [40]	D, MR	D, MR	D, C
Functional Assessment Staging (FAST) [39]	MR	D, MR	D, C
Neuropsychiatric Inventory (NPI) [54]	D, MR, O	D, MR, O	D, O
Cornell Scale for Depression in Dementia (CSDD) [56]	D, MR, O	D, MR, O	D, O
Physical Self-Maintenance Scale [182]	D, MR, O	D, MR	D, C
Instrumental Activities of Daily Living Scale [182]		D, MR	D, C
General Medical Health Rating [183]		D	D, C
Clinical Global Impression of Change [184]		O	

Table legends: D: Demographic section, MR: Used in medication reviews in I) COSMOS and II) LIVE@Home.Path, O: Outcome, C: Covariate.

3.2.1 Dementia severity

Mini-Mental Status Examination

MMSE is a 30-item screening instrument to assess cognitive impairment [40]. It is administered directly to the patient by trained health care personnel. MMSE covers orientation in time and place, registration, attention and calculation, recall, language, repetition and the ability to follow commands. A lower score indicates poorer cognition (range: 0-30). A score of 30 indicates no dementia, 26-29 questionable, 21-25 mild, 11-20 moderate, and ≤ 10 severe dementia [185], while scores ≤20 are highly characteristic of dementia [40]. The validity and reliability are good for assessing cognitive impairment in older people [40].

Functional Assessment Staging

FAST is a tool to assess the level of functioning in PwD regardless of etiology [39]. Supplemented by information from a knowledgeable caregiver, health care personnel

proxy-rate the level of the highest ordinal deficit elicited (range: 1-7); lower scores indicate better functioning [39]. A score of 1-2 indicates normal cognition, 3-4 mild dementia, 5 moderate dementia, and 6-7 severe dementia [186]. The validity and reliability are good for evaluating functional deterioration in PwD [186].

3.2.2 Behavioral and psychological symptoms of dementia

Neuropsychiatric Inventory

NPI is a widely used assessment tool for BPSD screening, and several versions exist [54]. We used the standard version (NPI-12) to assess BPSD in LIVE@Home.Path because it is suitable for proxy-rating by informal caregivers, while in COSMOS, we used the nearly identical Nursing Home Version (NPI-NH), as the questions are rephrased to reflect the professional relationship with the reporter. NPI assesses the frequency (1-4) and severity (1-3) of the 12 symptoms of BPSD listed in Table 1.2, p. 20, during the four preceding weeks [54]. For each domain, a score is generated by multiplying frequency and severity scores and equals 0 if the symptom is not present (range: 0-12). A score ≥4 indicates symptoms of clinical relevance [19, 53, 54, 187]. Paper I presents the domain scores, while Paper II and III also present subsyndromes (i.e., psychosis, hyperactive behavior, and mood) by summarizing domain scores according to the factor analysis in Table 1.2 [51]. All 12 domain scores are aggregated in the total NPI score (range: 0-144) [54].

The Norwegian version of NPI has good reliability and validity for assessment of BPSD in nursing home patients with or without dementia, with psychometric properties matching those of other translations [54, 188].

Cornell Scale for Depression in Dementia

CSDD is a 19-item tool for assessing depressive symptoms in PwD [56]. In the proxy-rater interviews, the informal or formal caregiver scores each item over the preceding week, from absent to severe (0-2), or 'symptoms not possible to evaluate' (a) [56]. The item scores are added to yield the CSDD total score (range: 0-38), and a score ≥8 indicates depression [56, 189].

The Norwegian version of CSDD has good reliability and validity for assessment of depressive symptoms in older people with and without dementia, in line with the international literature [189].

3.2.3 Other assessment tools

The participants' ability to perform ADL tasks were proxy-rated using the Physical Self-Maintenance Scale (range 6-30, a higher score indicates higher dependency) and Instrumental Activities of Daily Living Scale (range 8-31, a higher score indicates higher dependency) [182]. The Physical Self-Maintenance Scale assesses the ability to perform six areas of personal ADL (i.e., toileting, feeding, dressing, grooming, physical ambulation, and showering), while the Instrumental Activities of Daily Living Scale assesses the ability to perform in eight areas necessary for older adults to live independently at home (i.e., operating the telephone, shopping, preparing food, household management, doing laundry, independence regarding transportation, managing self-medication, and handling finances).

We adapted the Clinical Global Impression of Change to assess communication with the PwD's GP as perceived by the informal caregivers in LIVE@Home.Path [133, 184]. The adapted 11-point scale ranged from -5 'Very much worse' to 5 'Very much improved', via 0 'No Change' [133, 184]. Originally, the Clinical Global Impression of Change was developed for tracking patient progress and treatment response to pharmacological treatment evaluated by health care professionals [184].

3.3 Classification of drugs

In COSMOS, prescription data was extracted from the nursing home patients' medical records. The dyads in LIVE@Home.Path reported the PwD's drugs in current use including over-the-counter drugs. Data was confirmed from prescriptions, drug packaging, and medical records from the nursing home services, etc. We classified all substances listed in the Anatomical Therapeutic Chemical Index (ATC) as drugs [78]. Drugs administered in a fixed schedule were regarded as being in regular use, and all others on-demand. The total number reflects the sum of drugs in

use. N05A, N05B, N05C, N06A, and N06D per ATC qualified as psychotropic drugs (Table 1.3, p. 24).

3.4 Ethical considerations

3.4.1 Approvals and registrations

COSMOS, LIVE@Home.Path, and PAN.DEM obtained ethical approvals prior to patient enrollment (see 9.3.1, 9.4.1, and 9.5.1), respecting the Norwegian Health Research Act [190]. The Norwegian Centre for Research Data approved the assessment and utilization of personal data for the volunteers and volunteer coordinators affiliated with the nonprofit organizations in LIVE@Home.Path. The trials were registered on the online database ClinicalTrials.gov to secure research transparency. Table 3.2, p. 39, and Table 9.3, p. 120, list registration and approval details.

3.4.2 Consent

We recognize PwD as an especially vulnerable group, as they might have limited insight into their illness and capacity to comprehend the information relating to a trial. Consequently, they may lack the ability to accommodate the principal rule of express and informed consent for general research participation. In COSMOS, the informal caregiver or legal advocate acted as a consultee by providing presumed consent if the patient could not give valid informed consent. In LIVE@Home.Path, the PwD were more than less able to provide consent, considering the inclusion criteria. However, the informal caregiver spoke on the PwD's behalf when in doubt, reflecting the presumed will of the individual.

The informal caregivers provided informed verbal and written consent to participate in LIVE@Home.Path. In PAN.DEM, they consented verbally at the start of the telephone interview after receiving verbal information from the researchers and written information by a text message.

The Appendix contains the consent forms (see 9.3.2, 9.4.2, and 9.5.2). No participants received formal compensaton for participation.

3.4.3 Legal grounds for processing personal health data for research purposes

When COSMOS was conducted (2014-2015), ethical approval was considered to provide adequate legal grounds for processing personal health data for research purposes [191].

For LIVE@Home.Path, we also conducted a Data Protection Impact Assessment (DPIA) in compliance with the General Data Protection Regulation (GDPR) of 2018 governing the collection and processing of personal data in the European Union and European Economic Area [191, 192]. The legal basis for LIVE@Home.Path is secured in GDPR Article 6(1) (e: that the data processing is necessary for the performance of a task carried out in the public interest) and Article 9(2) (i: that the data processing is necessary for reasons of public interest in the area of public health; and j: that the data processing is necessary for archiving purposes in the public interest) [192]. This was the first DPIA completed at UiB (J. Veim, Data Protection Officer, personal communication), holding the UiB archive reference 2019/5569.

3.4.4 Patient and public involvement

WHO recommends user involvement of PwD and informal caregivers in studies considering dementia [193]. This section describes how we met this principle.

In COSMOS, user involvement was not systematically integrated with the design or management of the trial. However, we involved the user representative at SEFAS (R.S.), with the experience of being the husband of a PwD, first at home and later in a nursing home, by interpreting, and disseminating COSMOS results including Paper I.

In LIVE@Home.Path, we incorporated user involvement at all stages in the conduct of the trial [166, 177]. In the planning phase, the Norwegian Health Association represented the interests of people with dementia, while R.S. represented the informal

caregivers. Also, R.S. reviewed the consent forms, advised on recruitment, prioritized the assessment tools, consulted on how to collect data in the least obtrusive way, and made sure the protocol and intentions of the trial were respected. As the pandemic hit, we prospered on this structure for responsible research innovation, i.e., that scientific processes are developed taking the societal needs including changing circumstances and the potential impact of research into account [194]. R.S. prioritized assessment tools and designed questions for the PAN.DEM interview as well as the information provided to the informal caregivers upon recruitment and on adapting LIVE@Home.Path to the ever-evolving pandemic scenario [167].

3.5 Statistics

We present descriptive statistics in numbers (n) and percent (%), mean and standard deviation (SD), and median and interquartile range (IQR). Total scores were calculated without substitution for NPI and CSDD with >80% answered, otherwise regarded as missing. This also applied in handling incomplete MMSE data in COSMOS, yet not in LIVE@Home.Path, as a complete score was necessary for inclusion.

In Papers I and II, changes in primary and secondary outcomes between time points (number of psychotropic drugs and BPSD) were compared for the intervention and control groups using the unequal variances t-test. In Paper I, multilevel mixed-effect negative binomial regression was applied to model whether the observed changes in the number of prescribed psychotropic drugs resulted from time and local variations within the clusters. In Paper II, subgroup analyses comparing 1) those who had their medications reviewed to those who did not within a) the intervention and b) control groups and 2) completers and non-completers were made using Pearson's chi-square test for categorical data, the unequal variances t-test for normally distributed data, and the Wilcoxon-Mann-Whitney test for non-normal data.

In Paper III, changes in BPSD between the pre-pandemic and pandemic assessments were estimated using Wilcoxon matched-pairs signed-rank test. For the sum scores

(i.e., NPI total score and subsyndromes, CSDD total score) showing significant change, we utilized multiple logistic regression to explore which factors (covariates) were associated with change. We used the unequal variances t-test to address potential associations between these sum scores showing significant change and pre-pandemic factors (i.e., randomization and symptom-specific psychotropic drug use). To explore whether consecutive sampling introduced bias, we compared our PAN.DEM study sample to those not included yet still in the parent trial using two sample t-test, Wilcoxon-Mann-Whitney test, or Pearson chi-squared test.

We considered results with P-values <0.05 to be statistically significant. Missing data was handled with listwise deletion. We performed the analyses in Stata/IC, release 16 (StataCorp, 2019. *Stata Statistical Software: Release 16.* College Station, TX: StataCorp LLC) or 17 (StataCorp, 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC).

4. Results

4.1 Paper I

- From 723 enrolled, 428 nursing home patients not lost at four months were included (intervention group n=217; control condition n=211): 325 (76%) females; mean age 86 (SD: 7.6); mean MMSE score 12 (SD: 7.7).
- BPSD at baseline:
  - 288 (67%) patients displayed one or several symptoms of clinical relevance for NPI-NH, the domains of irritability and anxiety were most pronounced.
  - 175 (41%) patients had a CSDD total score indicating depressive symptoms of clinical relevance.
- Psychotropic drug use at baseline:
  - 307 (72%) patients used any psychotropic drug, while 67 (16%) used three or more psychotropic drugs regularly. Antidepressants were the drug class most often prescribed, given to 171 (40%) patients.
  - 268 (63%) used psychotropic drugs on-demand, predominantly anxiolytics.
- Impact of the intervention:
  - 74 (34%) in the intervention group discontinued at least one psychotropic drug (regularly or on-demand); the corresponding number was 30 (14%) among the controls. Similarly, 56 (26%) in the intervention group and 24 (11%) of the controls discontinued any regularly prescribed psychotropic drug. The highest reductions in psychotropic drugs were found among patients using several psychotropic drugs and for the drug classes most often prescribed.
  - The COSMOS intervention led to no deterioration in BPSD, comparing change within the intervention group to that of the controls.
  - The level of functioning improved overall for the intervention group and worsened in the control group.

Conclusion: In the multicomponent COSMOS intervention, medication reviews reduced the use of psychotropic drugs in nursing home patients with no deterioration in BPSD, while independence in personal ADL improved.

4.2 Paper II

- Of 438 assessed for eligibility, 280 home-dwelling PwD were included, of whom 237 participated at six months (intervention group n=67; control condition n=170): 149 (63%) females; mean age 82 (SD: 7); median MMSE score 21 [18, 23] and median FAST score 4 [4, 4].
- BPSD at baseline:
  - 159 (67%) PwD had ≥1 symptoms of clinical relevance for NPI-12; apathy was the most frequent. Mood was the subsyndrome with the highest median score.
  - 73 (31%) PwD had a CSDD total score indicating depression of clinical relevance.
- Psychotropic drug use at baseline:
  - 150 (63%) PwD used psychotropic drugs regularly, of which antidementia drugs were most frequently in use (n=112, 47%).
  - 17 (7%) PwD used psychotropic drugs on-demand, constituting antipsychotics, anxiolytics, and hypnotics/sedatives.
- Impact of the intervention over the six months:
  - The reach of medication reviews increased: GPs reviewed the medications of 44 (66%) in the intervention group and 72 (42%) of the controls.
  - Comparing changes in psychotropic drug use and BPSD in the intervention group to the controls, no differences were detected between baseline and six months.
  - Patient-GP communication was enhanced in the intervention group (mean score 0.95 [standard deviation 1.68] vs 0.41 [1.34]). The informal caregivers of those who had their medication reviewed reported improved patient-GP communication compared to those who did not have their medication reviewed, regardless of group allocation.

Conclusion: During the multicomponent LIVE intervention, medication reviews were conducted more frequently for home-dwelling PwD: the process induced no change in psychotropic drug use or BPSD between groups, while communication with the GP improved.

4.3 Paper III

- 104 home-dwelling PwD: 63 (61%) females; mean age 82 (SD: 7); median MMSE score 21 [18, 24] and median FAST score [4, 4].
- Pre-pandemic BPSD:
  - The median number of symptoms of clinical relevance on NPI-12 was 2 [0, 4]; apathy was the most frequent symptom, followed by irritability. Mood was the subsyndrome with the highest median score.
  - 34 (33%) PwD had a CSDD score indicating depression of clinical relevance.
- Impact of the Covid-19 restrictions:
  - Six to nine weeks into the restrictions, 32 (31%) of the PwD had contact with health care professionals postponed or averted; 42 (40%) experienced healthcare service changes; 29 (28%) had less contact with the informal caregiver; and 70 (67%) had partial insight into the pandemic situation.
  - Increase in numbers of BPSD with symptoms of clinical relevance (2 [0, 4] to 3 [1, 5]) and total score (16 [4.5, 29] to 20 [7, 32.5]) for NPI-12.
  - NPI-12 total score worsened in 57 (55%) of the PwD and was associated with postponed or averted contact with health care professionals (OR 3.96, 95% CI 1.05 to 14.95).
  - 37 (36%) of the PwD had increased scores on the NPI-12 psychosis subsyndrome; median increase from 0 [0, 3] to 0.5 [0, 6]. Partial insight into the Covid-19 situation (OR 9.57, 95%CI 1.14 to 80.71) and less contact with informal caregiver (OR 4.45, 95%CI 1.01 to 19.71) was associated with worsening.
  - Increase in depressive symptoms in the NPI depression domain (0 [0, 3] to 1 [0, 6]) and CSDD total score (5 [3, 9] to 7 [4, 12]). According to CSDD, 56 (54%) of PwD experienced worsening depressive symptoms, which was inversely associated with the use of on-demand psychotropic drugs (OR 0.16, 95%CI 0.03 to 0.75).

Conclusion: BPSD deteriorated in home-dwelling PwD during the Covid-19 restrictions; most pronounced for symptoms of psychosis and depression.

5. Discussion

This thesis aims to investigate the impact of medication reviews in multicomponent interventions, as well as the impact of the Covid-19 restrictions on BPSD in PwD. In the following, we first consider the internal and external validity of our findings concerning BPSD and psychotropic drug use before discussing the assessments, implementation, and statistical analyses in the related papers. The discussion of the specific results relates to four key points: symptom burden, drug use, medication reviews to improve drug use, and the Covid-19 restrictions.

5.1 Methodological considerations

Even though RCTs are considered the gold standard for evaluating the effect of interventions, the estimates can be prone to bias, i.e., systematic flaws in design, conduct, analysis, and reporting that lead to over- or under-estimation of the actual intervention effect [195].

5.1.1 Internal validity

High internal validity means that the differences observed between the groups in a RCT reflect the true effect of the intervention. The Cochrane Collaboration suggests the following domains for assessing the risk of bias in RCTs [195]:

Selection bias

A selection bias can occur if participants systematically differ in ways other than the intervention or exposure under investigation [196]. The risk of selection bias is reduced by randomization to ensure that the participants have an equal chance of being allocated to one or the other intervention groups [197]. Both COSMOS and LIVE@Home.Path utilized randomization. COSMOS was a cluster-randomized controlled trial (cRCT) with a traditional two-arm design utilizing a 1:1 intervention-to-control ratio. LIVE@Home.Path was a closed cohort stepped-wedge cRCT, i.e., a one-way crossover trial where all participants are recruited before randomization and exposed to both the control and the intervention period, and the timing is determined by randomization [198]. As the Covid-19 pandemic challenged implementation

during the second six-month intervention period (Figure 3.2), Paper II does not analyze the data according to the stepped-wedge design, but treats it as a two-armed trial with a 1:2 intervention-to-control ratio. The closed cohort design reduces the risk of selection bias caused by recruiters selectively enrolling patients into the trial based on what the next treatment allocation is likely to be. For each municipality, the study statistician generated a random sequence allocation with a pragmatic restrain securing that each of the three clusters included individuals from several geographical zones covered by a municipal coordinator. In COSMOS, the nursing home units recruited were already assigned to either the intervention or the control group by constrained complete list randomization weighted by geographic and monetary status, before the patients were invited to participate. This increases the risk of selection bias [197]. In both trials, however, the study statisticians generating the random allocation sequences did not disclose allocation status to the research staff and participants, to safeguard allocation concealment.

As shown in Figure 1 of Paper II, only 10% of the nursing home residents did not meet the COSMOS inclusion criteria, while the corresponding percentage was 18% in LIVE@Home.Path (Figure 2, Paper II). If the recruiters for LIVE@Home.Path invited PwD they believed would show the greatest reduction in resource utilization from the intervention, we are at risk of introducing selection bias to the primary outcome estimate [197]. Nonetheless, we find it less likely that the participants in both COSMOS and LIVE@Home.Path were selectively sampled based on their determination of whether the interventions would reduce levels of BPSD.

In PAN.DEM, the participants were selected by consecutive sampling; we invited the dyads to participate in the order in which they appeared in our files. This increases the risk of selection bias. We could have reduced this risk by randomizing their order in our files, for instance, using a random sequence generator. Nonetheless, we found minimal differences when comparing the demographical and clinical characteristics of the home-dwelling PwD in PAN.DEM to those not included, yet eligible in LIVE@Home.Path. This suggests that the non-random method of recruitment did not bias the estimates of the impact of Covid-19 restrictions [196].

Detection bias

Detection bias refers to systematic differences in how outcomes are assessed between study groups [199] and may arise when data collectors are aware of group allocation. In COSMOS, the proxy-rated data was collected by nursing home staff who knew which intervention the participants received, as they were the ones delivering the intervention, while in LIVE@Home.Path, the data collectors were blinded to allocation sequence when assessing proxy-rated BPSD in interviews with the informal caregivers. During the PAN.DEM assessment, the data collectors knew that the participants were affected by the Covid-19 restrictions. This increases the risk of detection bias, possibly over-estimating the impact of the Covid-19 restrictions on BPSD. However, the Covid-19 restrictions left the informal caregivers not living with the PwD with even less basis for observation. We conducted an additional analysis, confirming that the informal caregivers not living with the PwD were more inclined to answer 'symptoms not possible to evaluate' on CSDD (data not shown). Consequently, we are at risk of systematically under-estimating BPSD by applying the 20% missing rule with no substitution (as is common practice in the field) [14, 142, 200]. As such, this introduces a greater detection bias in the BPSD estimates for the PwD living alone, possibly under-estimating the effect of the Covid-19 restrictions in this group.

Performance bias

The risk of performance bias increases if participants receive differing treatment or care in a trial because allocation is exposed [201]. It typically occurs when it is impossible to blind the participants or study personnel because the intervention can be easily distinguished from control conditions. This could impact the estimates of Papers I-III. A systematic review identified a lack of blinding of participants and data collectors as the most common threat to internal validity in cRCTs in primary care [202]. If subjective outcomes, defined as outcomes relying on judgement, are used, performance bias can be reduced by blinding the outcome assessors [201]. This strategy was applied to assessing patient-GP communication in LIVE@Home.Path in Paper II. The effect of performance bias can be further reduced by using an objective measure, such as the number of drugs in use. While proxy-rating is a generally good

option, considering the nature of dementia, it can never be viewed as an entirely objective measure. In COSMOS, BPSD were assessed and rated by those who also delivered the intervention and thus knew the allocation status, which increases the risk of over-estimating the intervention effect. In LIVE@Home.Path, the informal caregivers reported BPSD symptoms to data collectors blinded to allocation status, but it was impossible to blind the dyads to the coordinator-facilitated add-on LIVE intervention. The Hawthorne effect describes the observed improvement in behavior, not because of the intervention's efficacy, but rather as the participants are aware that they are under study [203]. The PwD in LIVE@Home.Path might not have recognized their allocation status, suggesting a low risk of the Hawthorne effect. In contrast, the informal caregivers in both allocation groups might have become more aware of symptoms and may consequently have reported higher levels at the follow-up assessment, undermining the potentially positive effects of the intervention on BPSD. This risk might be even higher during the intervention period as the allocation status was exposed to the informal caregivers reporting BPSD at the start of the intervention period, when their coordinator contacted them, and as the caregivers acquired knowledge of dementia.

Performance bias can also occur when the protocol is insufficiently implemented and adhered to, pp. 67-68 [154, 195].

Attrition bias

Attrition bias refers to systematic differences between participants leaving and continuing in a study as it progresses, applying to both RCTs and observational studies [204]. Figure 1 of Paper I and Figure 2 of Paper II show that the attrition was 15% for both COSMOS and LIVE@Home.Path. In the case of inadequate concealment of allocation in traditional parallel RCT, enrolled participants are at risk of withdrawing their consent if they are not allocated to the intervention group if their participation in the trial is motivated by the expected benefit of the intervention. The stepped wedge design is particularly suited to reduce this risk, as all participants will receive the intervention and, consequently, the expected benefit of the intervention. We found no indications that losses to follow-up occurred differently across the

intervention and control groups of Papers I and II. We performed complete cases only analyses in Papers I-III; consequently, the estimates of the intervention effect have higher internal validity for the participants still in trial at follow-up, relative to those included at baseline. Participants lost to follow-up due to transition to permanent nursing home care in LIVE@Home.Path had higher NPI-12 total scores and more frequent symptoms of clinical relevance compared to those still in trial constituting the Paper II sample, which increases the risk of under-estimating the impact of the LIVE intervention on the number of psychotropic drugs and BPSD.

Reporting bias

Reporting bias arises when research is disclosed selectively, depending on the results [205]. Transparency is the most critical action to mitigate this spurious tendency. The COSMOS and LIVE@Home.Path protocols were prospectively registered and published [128, 166]. Notably, the primary outcome of these trials was quality of life (COSMOS) and resource utilization (LIVE@Home.Path), while the change in BPSD and drug use were secondary outcomes. PAN.DEM explored unintentional outcomes of the Covid-19 restrictions, and we published a paper on the process development of the pandemic cohort [167]. Nonetheless, we did not have the predefined plan for analysis reported in Paper I-III, increasing the risk of reporting bias.

5.1.2 External validity

External validity refers to the extent to which (internally valid) results can be generalized or reasonably applied to “real world” populations [206]. This subsection considers issues with the potential to affect the external validity of our results.

Setting

Dementia affects people worldwide yet inherent differences in care organization between countries might limit the generalizability of our findings to Norway and countries with similar health care services. The definition of ‘nursing homes’ varies internationally, but a systematic review found that the term encompassed a relatively homogenous sample worldwide with regard to BPSD [19].

Even though health care services provided to home-dwelling PwD depend on the country, most PwD who live at home are attended by informal caregivers and GPs [21], which supports the high generalizability of our findings of improved patient-GP communication in Paper II. Added to this, PwD enrolled in the primary and secondary health care services were recruited. Both COSMOS and LIVE@Home.Path recruited participants from multiple sites within municipalities of various sizes across Southern Norway, thereby increasing the generalizability of the findings in Papers I-III. Finally, the physicians conducting the medication reviews in COSMOS and LIVE@Home.Path were not experts in the field of psychotropic medication review and deprescribing in PwD, which increases the external validity of findings in Paper I-II.

Sample

Highly restrictive entry criteria in a trial will reduce the generalizability of the findings, as the recruited sample may no longer be representative of the target population [206, 207]. This thesis concentrates on BPSD, even though a diagnosis of dementia was not an inclusion criterion in COSMOS, enrolling a considerable number of nursing home patients. Although the prevalence of dementia in Norwegian nursing homes approximates 85% [13, 208], a study showed a low diagnostic rate as mere 55% of residents with dementia according to the clinical dementia rating had a formal diagnosis of dementia in their medical records [208]. In Paper I, we included all residents in the nursing homes, but used the term BPSD to describe the level and change in symptoms, regardless of prevalence of dementia. We performed sensitivity analyses to evaluate how more restrictive classifications of dementia impacted our results [19]. Restricting the sample to those with MMSE scores ≤25 (indicating dementia [185]) (n=367) or MMSE scores ≤20 (highly characteristic of dementia [40]) (n=330) did not change the intervention effect regarding psychotropic drug use, BPSD, or personal ADL (data not shown). Restricting the sample to those with a diagnosis of dementia in their medical records, the intervention effect on antidepressants and personal ADL was no longer significant (n=274, Table 9.2, pp. 118-119). This could indicate that the results of Paper I may be generalizable to a

general nursing home population [130] and not specifically PwD, yet we cannot exclude that the differences are due to lower statistical power.

In LIVE@Home.Path, we applied different eligibility criteria. Dementia severity was assessed on enrollment, yet the self-reported etiology was not validated by medical records or diagnostic procedures [13, 38]. The diagnostic workup required for participation, p. 42, did not deviate much from clinical practice, which increases the external validity of the findings of Papers II and III [206]. We find it less likely that people without a dementia diagnosis would self-recruit to a trial on dementia care, but if so, we are at risk of including people with lower levels of BPSD and psychotropic drug use, which would make finding an intervention effect on these outcomes less likely. A study reported low disclosure and formal diagnosis of dementia in a representative sample of older adults receiving domiciliary care in Norway, which could indicate that the syndrome is either not recognized or not communicated to the formal and informal caregivers [38]. In LIVE@Home.Path, we mostly recruited participants through convenience sampling from geriatric and gerontopsychiatric out-patient clinics and municipal memory teams, which restricts the generalizability to PwD somehow attended by formal and informal caregivers. To increase generalizability, we could have drawn a random sample of PwD with a formal diagnosis by utilizing national registries such as NorCog [209], KUHR [210], or later, PraksisNett [211], yet we considered that this would not be possible for logistical, practical, and possibly ethical reasons.

To ensure the external validity of COSMOS and LIVE@Home.Path, municipalities of various sizes and located in urban and rural areas across the country were recruited. Additionally, Bærum and Bergen participated in both cRCTs, strengthening comparisons between the nursing-home and home-dwelling settings. However, the principal investigator did not recruit municipalities by random selection, but from her network in which previous trials also focusing on drug use in PwD had recently been conducted. Consequently, we suggest that our findings might under-estimate the national pre-pandemic psychotropic drug utilization and BPSD symptom load because the selected municipalities might be more inclined to implement non-

pharmacological treatment approaches for BPSD, compared to Norwegian municipalities overall.

Follow-up

The external validity of RCTs might be compromised by the inadequate duration of intervention and/or length of follow-up [206]. In COSMOS, the medication reviews were conducted during the two first months, thereby providing the physician with an opportunity to evaluate and change drug use before the four-month assessment [129]. In LIVE@Home.Path, we do not have data for how and when the medication reviews were conducted, challenging the interpretation of the external validity of the findings of Paper II. We consider medication review to be the most active component of COSMOS and LIVE, immediately effectuating changes in psychotropic drug use, yet not necessarily BPSD, and therefore the relatively short follow-up might reduce the external validity of the findings relating to BPSD of Papers I and II.

Differences between intervention and care as usual

COSMOS and LIVE@Home.Path implemented the combination of multiple intervention components recommended in clinical practice as an add-on to care as usual, increasing the external validity of the findings of Papers I and II [207, 212, 213]. The COSMOS intervention was based on WHELD and the method of conducting medication reviews advocated by the Norwegian Patient Safety Campaign [142, 214], while LIVE was designed to meet the requirements of the Dementia Plan 2020 [2]. Furthermore, the controls received care as usual with no prohibition of treatment, providing realistic comparisons while ensuring that the participants received the current best practice [206].

Restrictions were implemented all over the world during the initial phase of the Covid-19 outbreak. We therefore suggest that the estimates of the impact of the Covid-19 restrictions presented in Paper III have high external validity for other populations in other countries with similar healthcare services.

5.1.3 Assessments

Both the internal and external validity of our findings rely on whether the outcomes are clinically relevant and how they are assessed.

Assessment of BPSD

BPSD describe behavioral and psychological changes occurring over the dementia course and as such are regarded as symptoms originating due to the dementia syndrome. Although often used interchangeably, the term 'neuropsychiatric symptoms' encompasses similar symptoms not exclusively presented in PwD (Figure 5.1) [25, 187, 215]. Even though we reproduced the main findings with more restrictive classifications of dementia in the nursing home sample under COSMOS, p. 61, we acknowledge use of the term 'BPSD' as a limitation to Paper I.

Figure 5.1 BPSD relative to the broader term of neuropsychiatric symptoms

NPI is a comprehensive assessment tool that has become so popular since it was launched in 1994 that it now more or less defines changes regarded as BSPD [216]. However, NPI does not assess all psychiatric symptoms described in dementia. Changes in sexual demeanor, for example, are covered by the CMAI, a 29-item inventory devoted to agitated behavior [57]. As the CSDD baseline scores in both COSMOS and LIVE@Home.Path were higher than CMAI (data not shown), we decided to use CSDD, and not CMAI, in addition to NPI.

In this thesis, BPSD are proxy-rated by nursing home staff (Paper I) or informal caregivers (Papers II-III). NPI is an inventory that allows for proxy-reporting of symptoms only, while CSDD also allows for self-reporting, particularly by less cognitively impaired respondents. CSDD shows strong interrater agreement between self- and proxy-rating in cognitively impaired nursing home patients, supporting the use of a proxy in the assessment of BPSD, regardless of the severity of cognitive impairment [217]. Additionally, CSDD addresses the emotional state and thought content to a greater extent than inventories such as NPI and CMAI which focus on

the discrimination and quantification of more objective symptoms evident to the caregivers. The method of observation is straightforward, but challenges arise in settings in which continuous observation is less feasible (e.g., at-home vs. nursing homes, and pre-pandemic vs. pandemic settings) [58]. These factors reduce the strength of the findings in Paper II and III. However, baseline data from COSMOS indicates that even skilled raters report less sleep disruption using NPI and CSDD than indicated by continuous actigraphy data [218]. A systematic review identified a small, but rapidly growing body of evidence suggesting that data from sensors is valid for BPSD assessment [219].

NPI allows the rater to evaluate whether the symptoms in question occur from dementia, while CSDD does not make such considerations. We recognize that the informal caregivers, equaling family and close friends, are better equipped to judge whether the symptoms changed as a consequence of dementia, while the NPI-NH interview more or less excludes contributions from the (in)formal caregivers [54]. The findings of Papers I-III confirm previous reports that the depression domain of NPI and CSDD correlate well [72, 220], increasing the external validity of our findings [54].

Even though informal caregivers are more familiar with the PwD and are therefore likely to better evaluate whether a symptom can be attributed to the dementia syndrome, they might be less skilled than formal caregivers in distinguishing symptoms. Therefore, we paid close attention to the training and supervision of the data collectors in LIVE@Home.Path. Additionally, we decided to use a factor analysis to cluster symptoms on NPI into three subsyndromes (i.e., psychosis, hyperactive behavior, and mood) to increase the robustness of our findings. We applied the subsyndromes reported by Aalten et al. in Paper II and III [51], as this is the most cited factor analysis [50], conducted in a sample of Dutch home-dwelling PwD, showing similarity with the participants in LIVE@Home.Path [51].

How BPSD should be differentiated and quantified in the short term between clinical and research visits is debated [187]. NPI addresses symptoms over the preceding four

weeks; and CSDD over the past week. One naturally does not know what happens between assessments. Moreover, as symptoms tend to fluctuate over time [15], this is particularly challenging when evaluating the effect of interventions targeting BPSD. To best monitor BPSD in relation to treatment response, one should frequently apply validated psychometric scales and operationalize the scores according to established procedures, possibly aided by sensor technology for increased objectivity and precision [219]. In PAN.DEM, we narrowed down the time between assessments to a mean of 12 weeks (86 days, SD 19). As both NPI and CSDD indicated an increase in symptom levels, we suggest that our findings in Paper III have high external validity. However, the non-standardized frequency of assessment may also compromise comparisons with other studies evaluating the course of BPSD over time and in relation to treatment. For instance, assessments were carried out at nine months in WHELD [142] and yearly in DemWest [53].

Assessment of psychotropic drugs

In all papers, we collected data on all drugs currently in use – not the actual use. We consider the medical records of nursing homes to be accurate, yet in Paper I we do not know how often the patients refused scheduled drugs and how often they used drugs on-demand. In LIVE@Home.Path, we had drug use by self-reporting confirmed from prescriptions, drug packages, multi-dose drug dispensing, and medical records. However, we consider this data to be less accurate than the data of Paper I. As the method for data collection did not differ between assessments, this does not affect the estimates of change in Papers I and II, yet, we are at risk of over-reporting the drug use of nursing home patients while underreporting in the home-dwelling context.

While the classification of 'psychotropic drugs' by ATC differs slightly [89, 93, 95, 102, 105, 106, 130, 145, 221], the Neuroscience-based Nomenclature was launched in 2014, reforming the naming conventions for psychotropic drugs by neuropsychopharmacology rather than disease [222, 223]. The nomenclature describes psychotropic drugs in 10 pharmacological domains [223]. In Paper I-III, we

classified psychotropic drugs by ATC in order to compare our findings with previous research [78]. Nevertheless, we presented the results of Papers I and II in posters utilizing the Neuroscience-based Nomenclature, revealing minimal differences between classifications [224, 225].

5.1.4 Implementation

The protocols of COSMOS and LIVE@Home.Path allowed for continuous optimization of the implementation process in the local setting. Staff and coordinators gathered for midway evaluations to discuss promotors and barriers towards implementation [129, 166], applying a three-tiered red/amber/green rating system to evaluate implementation status. They were asked to state one aspect they perceived as difficult (red), two aspects they had succeeded with to some degree (amber), and three aspects that they had succeeded with (green) in implementing the multicomponent intervention. This approach has become popular in pilot studies [226, 227] and was chosen to collect and exchange experience. We assessed penetration and fidelity by patient logs and checklists [128, 166], and advocate that this structured evaluation also promoted acceptability, fidelity, penetration, and even sustainability (Text box 1.3, p. 33) [156, 228], as those facilitating the intervention learned from each other. Applying measures of implementation outcomes and theoretical approaches to implementation science could have captured additional provider attitudes, behaviors, contexts, and mechanisms of change [136, 156, 228]. However, COSMOS and LIVE@Home.Path were effectiveness-implementation trials primarily focused on effectiveness outcomes, while addressing ‘implementability’ in parallel [157]. In general, pragmatic elements may compromise the replication of research, effect size, and internal validity, yet yield stronger external validity than traditional RCTs [229] .

Considering medication reviews specifically, we hold more detailed information on implementation in COSMOS than in LIVE@Home.Path. In COSMOS, the process was rigorously documented by structured feedback during the midway evaluation, remarks in the patient logs, and feedback channeled to the researchers providing collegial support for the revisions [129]. As most of the physicians conducting the

medication reviews in COSMOS were GPs with visiting hours at the nursing homes, we suggest that the barriers emerging through simple thematic analysis (e.g., new and difficult instruments, lack of competence, practical challenges with changing drug regimens, and lack of time) also apply to general practices [129]. In LIVE@Home.Path, we relied on the dyads' self-reporting. However, the coordinators reported that medication reviews were some of the easier components to facilitate, because the electronic medical records enabled collaboration and also as the dyads were ready to attend their regular GP.

The Covid-19 restrictions were continuously evaluated as the outbreak evolved [230-232]. This evaluation was highly dependent on infection control. The Norwegian authorities have established a commission to review the management of the pandemic [233]. We are not aware that systematic process evaluations to consider implementation outcomes have been conducted, except for acceptability and appropriateness in public opinion services [234, 235]. However, the Norwegian Institute of Public Health has launched a priority project to provide retrospective knowledge concerning the consequences of key Covid-19 restrictions, including the preparation of research protocols that can be implemented to provide prospective data on the effectiveness of measures in the event of future infection waves [236]. Meanwhile, in PAN.DEM we were able to document indirect consequences of the implementation of Covid-19 restrictions during the first wave, i.e., the extent to which the informal caregivers had changed the level of contact with the PwD, and the consequences for healthcare services and volunteer support. We found that 56% of the caregivers did not live with the PwD, while only 28% reported reduced contact, suggesting that not all informal caregivers complied with the restrictions.

5.1.5 Statistics

In addition to bias, it is important to assess the precision of the estimates (the extent to which study results are free of random error) [195]. As Papers I-III are substudies of larger trials, the power calculations were conducted to target intervention effects of outcomes other than those investigated in this thesis [128, 166]. PAN.DEM was a cohort study with no sample size agreed on prior to recruitment; we sought to include

as many dyads as possible before the Covid-19 restrictions were eased, so as to investigate their impact on home-dwelling PwD [167]. Secondary analyses increase the risk of both type I (rejecting the null-hypothesis of no difference when it is true based on false-positives) and type II errors (accepting the null-hypothesis when it is not true based on false-negatives). In Paper II, the chance of type I errors increases due to multiple testing in the subgroup analyses to compare characteristics across groups, by medication review status and attrition. Furthermore, the Covid-19 restrictions led to misbalanced group sizes, increasing the risk of type II errors. We are therefore at risk of drawing our conclusions on the basis of type II errors, which could have been mitigated if we had been able to utilize the stepped-wedge design as intended.

NPI domain scores are non-continuous and non-normally distributed variables as zero symbolizes the symptom not present, and the numbers 5, 7, and 11 are lacking. The NPI total score is a sum score with a skewed, right-tailed distribution, which causes problems when using parametric methods [237]. We did not consider this on designing the descriptive statistics in Paper I, presenting the baseline BPSD scores by mean (SD), while in Papers II and III we present BPSD and psychotropic drugs by median [IQR]. The fact that the participants were explicitly sampled for neither BPSD nor psychotropic drug use might have inflated the skewed distribution. However, this might be more prominent in the home-dwelling setting, as BPSD are consistently associated with nursing home placement. The outcome of interest, however, was the change in BPSD and psychotropic drug use, and assuming that the change between two assessments would be normally distributed, we used Welsh's unequal variances t-test to compare the change between groups (incorrectly reported in Paper I, see p. 80 for details).

To assess change in BPSD between groups in Papers I and II, we chose Welsh's unequal variances t-test over independent samples t-test, because it is more robust, limiting the risk of type I errors for unequal variances and unequal sample sizes under normality. We performed a multi-level mixed-effect negative binomial regression to investigate whether the reductions in psychotropic drug use were associated with time

and nursing home unit variations. Such analyses were not considered for Paper II, as the initial analyses indicated no changes in prescribing practices.

In Paper III, we used the Wilcoxon matched-pairs signed-rank test to compare differences in BPSD – presented by medians on NPI and CSDD – before and during the Covid-19 restrictions. We found that all sum scores with a statistically significant change between the pre-pandemic and pandemic assessment signified a worsening of symptoms. We therefore collapsed change in the sum scores to binary in the regression analyses when exploring factors associated with worsening. We could have defined clinically meaningful change before commencing data analyses along the lines of the threshold for clinical relevance on NPI and CSDD [238]. Such a strategy would probably yield fewer PwD with worsening BPSD, as those with severe or very severe [53] symptoms would not be classified with a clinically significant worsening. Alternatively, we could have employed other regression models not necessitating a dichotomous dependent, to explore factors associated with symptom change during the pandemic. However, we opted for logistic regression due to the limited sample size and our main research question: do PwD experience more severe BPSD during the pandemic?

Papers I-III only include two assessments of BPSD, making evaluation of change at group level more relevant than exploring the symptom course in individuals. Analyzing BPSD data at group level makes our findings easily generalizable to the population from which the sample was drawn and further eases the comparison of the intervention effect with other studies. If we had followed PwD with several data points, we could have addressed the symptom trajectories [15, 52, 53] or even summarized the data in an interrupted time series analysis [239].

5.2 Discussion of the specific results

5.2.1 Levels of and changes in BPSD

BPSD are predictors of nursing home placement [240-242]. In this thesis, we report higher levels of BPSD in nursing homes than at-home, in addition to higher scores

and numbers of clinically relevant BPSD in PwD transferred to permanent nursing home care (Paper II). Nevertheless, the baseline levels for home-dwelling PwD in 2019 (Paper II) are close to what was previously reported on admission to Norwegian nursing homes in REDIC 2012-2014 [94], which might indicate that PwD now dwell at home for longer, in line with political goals [193].

The levels of and changes in BPSD scores differ between studies, according to assessment, study design, setting, and sample [19, 52]. The DemWest cohort recruited patients with early-stage dementia from general practice, revealing an increase in the mean NPI total score from 15 to 17 during the first five years after dementia diagnosis; a change not likely of clinical relevance [15]. For comparison, the reported increase in NPI total score from 16 to 20 during the first months of the Covid-19 restrictions (Paper III) was still small, yet substantial, and developed over a much shorter period. Furthermore, when assessed every six months, the NPI psychosis subsyndrome score was mainly unchanged during the first 2.5 years of nursing home admission in REDIC [243], substantiating our findings of worsening psychotic symptoms being a consequence of the restrictions. Another Norwegian longitudinal cohort study found no changes in the psychosis subsyndrome or the total NPI score on following nursing home residents with dementia for more than four years [14]. Considering CSDD, the change we report in Paper III is in line with the increase in depressive symptoms following the randomized discontinuation of antidepressants in 128 nursing home patients with dementia selected by their presentation of BPSD, while being prescribed antidepressants for three months or more, in the DESEP study [200]. Correspondingly, a network meta-analysis found the efficacy of interventions such as multidisciplinary care and occupational therapy for depression in PwD to be of the same magnitude as the deterioration we document in PAN.DEM [72].

5.2.2 Levels of and changes in psychotropic drug use

Except for antidementia drugs, we report a lower proportion of psychotropic drug users among home-dwelling PwD than among nursing home patients. Our findings substantiate that drug use differs according to care level, as found in a cross-sectional

observational study from Oslo, Norway [244]. In the DemWest cohort, the use of antipsychotics, hypnotics/sedatives, and anxiolytics at the time of dementia diagnosis (2005-2013) resembles our 2019 findings for home-dwelling PwD with slightly more advanced dementia (Paper II), while the proportion taking antidepressants was close to what we report for nursing homes in 2014-2015 (Paper I) [93]. Our findings align with trends showing decreased use of antipsychotics to alleviate BPSD over the last decades, although often replaced with other psychotropics, especially antidepressants [101-103]. A systematic review of psychotropic drug use found that the rates of antipsychotic drug prescription for PwD were the lowest in Western Europe [89], while a retrospective cohort study from England found that continuity of GP care was associated with safer prescribing for PwD regardless of residency [245]. Psychotropic dispensing rates increase following a change in GP when entering nursing home care [94, 246], underscoring the importance of the regular GP scheme for the relatively lower use of psychotropic drugs among home-dwelling PwD.

5.2.3 Medication reviews to improve psychotropic drug use

The Norwegian Directorate of Health registered that 32% of home-dwelling PwD in Norway had a GP-conducted medication review in 2018 [247]. It is likely that not all medication reviews conducted in routine practice are registered, partly due to formal requirements for using the reimbursement code, such as the presence of polypharmacy [25, 125, 247]. We argue that our finding of 40% of our home-dwelling PwD reporting that they underwent a medication review in the preceding six months (Paper II) reflects the current general Norwegian practice.

In recent years, public awareness of the over-prescribing of psychotropics in PwD has served as an incentive to embed medication reviews in the multicomponent interventions in COSMOS and LIVE@Home.Path. However, this incentive may also have changed the Norwegian psychotropic prescribing in such a way that further reductions are difficult to achieve and potentially unwarranted. Paper I illustrates that the highest number of psychotropic drug reductions was found among patients who received several drugs at baseline. Other factors could also explain why medication reviews led to successful psychotropic deprescribing in Paper I and not in Paper II:

- **Collegial support**: The collegial support provided to nursing home physicians at the COSMOS multidisciplinary meetings ensured rigorous, systematic evaluations of the appropriateness of therapy. The researchers providing the collegial support sought to keep the advice and degree of participation consistent between the nursing homes included and over time [248]. As this form of mentoring is highly resource intensive, we did not provide the GPs in LIVE@Home.Path with independent perspectives and sparring from peers. However, the COOP trial, which included 174 home-dwelling older Norwegians receiving polypharmacy, showed more drug withdrawals and reduced dosages when regular GPs were provided with support from geriatricians when conducting medication reviews [249]. Clinical pharmacists are less integrated into dementia care in Norway than in several other countries [129, 250], yet could also assist with medication reviews [251], exemplified in COSMOS. The nursing home physicians in COSMOS reported that the interprofessional discussions helped to facilitate difficult decisions on treatment [129], which might explain why the medication reviews in Paper I resulted in successful psychotropic deprescribing, yet not in Paper II.
- **Systematic assessment of symptoms**: As highlighted in the background, we propose an individual and structured evaluation of BPSD (Figure 1.2). Even though every participant was assessed systematically prior to the medication review in LIVE@Home.Path, we do not know the extent to which the GPs used the clinical reports, while in COSMOS, the nursing home physicians evaluated treatment with colleagues and used the assessments systematically. This could partly explain why the medication reviews conducted in COSMOS (Paper I) only reduced psychotropic drug use, and not in LIVE@Home.Path (Paper II).
- **Allocation concealment**: The nursing home physicians knew that their wards were to participate in COSMOS well in advance. In contrast, a request to revise pharmacotherapy informed the GPs that their patients were included in LIVE@Home.Path and to receive the intervention. This approach to encouraging the GPs resembles that of a pragmatic cRCT to examine the effectiveness of an educational deprescribing intervention in primary care for 3,012 older Americans

with cognitive impairment taking five or more long-term drugs [235]. While LIVE@Home.Path was conducted, a GP contacted the research group, expressing disappointment that he was not involved earlier, as he felt that his mandate was somewhat unclear. We discussed involving or consulting the PwD's GP at the trial incision, as in other successful deprescribing studies [249, 252]. However, we feared this would increase the risk of contamination between groups, reduce the generalizability, and be resource intensive for the research team. Nonetheless, we recognize that this approach could have yielded insight into barriers and promotors, standardization of the medication review process, and collegial mentoring in general practice.

We evaluated the impact of medication reviews in COSMOS and LIVE@Home.Path by the number of psychotropic drugs used and BPSD, which we regarded as clinically relevant outcomes for Papers I and II. In addition, we could have evaluated the medication reviews by applying process measures. For instance, we could have judged the interventions' success by the explicit measure of appropriateness (Table 1.4) applied by the physicians for decision support, p. 40 and p. 128. STOPP 2, however, receives criticism for its limited ability to prevent serious adverse drug events applicable to older adults with multimorbidity, including dementia [112].

Neither COSMOS nor LIVE@Home.Path was primarily designed to improve psychotropic drug prescription for BPSD in PwD; this issue has been explored in other cRCTs [110, 142]. In PROPER II, structured multidisciplinary medication reviews were repeated every six months for 18 months in Dutch nursing homes [110, 253]. Reviewing medication improved the appropriateness of psychotropic drugs, including antidementia drugs, while the prevalence of psychotropic drug use prescribed for BPSD increased from 50% to 55%. In comparison, the prevalence decreased from 50% to 42% for those PwD receiving care as usual [253]. The occurrence of BPSD remained stable in both the intervention and control groups during the 18-month follow-up. The PROPER intervention mainly addressed psychotropic drugs, rather than the underlying causes for prescription and other factors relevant in the prescription process. The authors therefore suggested future

studies to enrich revisions with components that address personal attitudes and communication not only relating to the prescription of psychotropic drugs, but also to BPSD [253]. An example of the success of such enrichment is found in WHELD, which explored the effect of antipsychotic review alone, or in combination with social interaction or physical exercise, for 277 PwD residing in 16 UK nursing homes [142]. Antipsychotic review alone led to a reduction of antipsychotic drug use by 50% from 18% at baseline, yet this led to a deterioration in overall BPSD, while the concurrent delivery of social interaction mitigated this detrimental impact. The exercise intervention significantly improved overall BPSD, but not depressive symptoms [142]. These findings from WHELD are comparable with our findings in Paper I, in which we did not find a worsening of BPSD among nursing home patients on reducing the use of psychotropic drugs while also receiving the other non-pharmacological components of the COSMOS intervention.

Only one comparable cRCT has been performed in the home-dwelling setting. The Delphi-MV trial provided 407 cognitively impaired Germans living at home with dementia care management, including interdisciplinary case conferences [252]. This model for collaboration in primary care did not affect PIM, but increased the use of antidementia drugs and reduced BPSD compared with care as usual [252], contrasting with our findings in Paper II.

Even though we boldly state that ‘less is more’ in the title of Paper I, PwD are also at risk of being exposed to under-prescription, although most pronounced for cardiovascular, anticoagulant, and anti-osteoporotic drugs [98, 244]. A narrative review of under-prescription in older adults suggests a prevalence of up to 70%, which is associated with multimorbidity, polypharmacy, dementia, and the absence of specific clinical trials in older patients [98]. It further suggests using process measures not merely focusing on drugs to avoid, such as START and FORTA (Table 1.4), in comprehensive geriatric assessments for which prescriptions should be individualized. This also applies to PwD challenged by BPSD, and we therefore

emphasize individual and repeated evaluations of overall drug use in balancing the twin traps of overprescribing and therapeutic nihilism in dementia care.

5.2.4 Impact of the Covid-19 restrictions on BPSD

In Paper III, we document an increase in BPSD in the initial phase of the Covid-19 restrictions. In theory, the progression of the dementia syndrome itself could cause this deterioration. However, due to the relatively large increase in BPSD over a corresponding short period, we argue that the deterioration in BPSD is a consequence of the pandemic restrictions, including withdrawal of psychosocial support and interaction with others (as discussed on p. 68). Our findings furthermore align with the growing body of evidence showing deteriorating BPSD during the initial phase of the pandemic (Table 1.6, p. 35) [165]. We found the most pronounced increase in the symptoms of psychosis and depression, yet the literature on specific symptoms is inconsistent, suggesting an increase in the full spectrum of BPSD, ranging from agitation and aberrant motor behavior to apathy [169-171]. Although some studies indicate the beneficial effects on BPSD of lifting the restrictions [170, 171], the long-term impact of the pandemic scenario is not captured at the time of writing [165].

Interestingly, we find that the odds for worsening psychosis increased tenfold with partial insight into the Covid-19 situation, relative to no or full insight, while no association was evident between the degree of insight and the increase in overall BPSD or depressive symptoms. A prospective cohort study which included 38 home-dwelling PwD during the first Italian lockdown indicated that PwD still perceived stress, even if they did not have insight into the situation [254]. The perceived stress was significantly associated with their cognitive reserve, which is in line with our findings suggesting that dementia severity evaluated with MMSE and FAST was associated with a worsening of BPSD (Paper III, Table 4).

We propose that the main reason for exacerbating BPSD was the loss of social contact with both formal and informal caregivers [255], as well as the withdrawal of ‘non-essential’ health care services [256, 257]. This highlights the importance of continuous care provided as usual to PwDs residing at home – in other words,

compromising care as usual (i.e., the control condition) impacted BPSD. In contrast, the add-on multicomponent LIVE intervention did not impact BPSD. Albeit not primarily designed to alleviate BPSD, we suggest that multicomponent, complex interventions such as COSMOS and LIVE would probably reduce BPSD when compared to a do-nothing group, instead of care as usual which, from a research perspective, represents an ethical dilemma. Moreover, this suggests that health care providers and caregivers of PwD should pay particular attention to over- and under-stimulating environments as predisposing factors when evaluating BPSD, as outlined in Figure 1.2.

6. Conclusions and future perspectives

In this thesis, we have prospectively investigated the impact of medication reviews in the multicomponent interventions of two large cRCTs and the consequences of the Covid-19 restrictions on BPSD in a cohort study. We found that BPSD deteriorated in the initial phase of the Covid-19 restrictions for PwD residing at home, but the symptoms were not impacted by medication reviews concerning nursing home patients and home-dwelling PwD. The Covid-19 pandemic and related policies changed the biopsychosocial aspects to a greater extent than can be expected from scientific experiments, which highlights that in order to evaluate the outcome of implementation-effectiveness trials, it is crucial to safeguard and evaluate the implementation process. We found that medication reviews using collegial mentoring and systematic clinical evaluation in COSMOS led to safe deprescribing of psychotropic drugs in nursing homes, most pronounced for those receiving several drugs, while medication reviews in general practice did not affect psychotropic drug use. Notably, the LIVE intervention increased the reach of GP-conducted medication reviews, showing that when encouraged, they increase the reach of reviews for home-dwelling PwD, leading to better communication.

By supplementing COSMOS and LIVE@Home.Path with data from PAN.DEM, this thesis provides physicians and policymakers with evidence from real-world dementia care on which to base their decisions [207]. It draws attention to the relative importance of practices already established to manage BPSD over the dementia course, such as medication reviews, communication with GPs [258], and support from formal and informal caregivers. Our findings regarding the impact of the Covid-19 restrictions have implications for future pandemic policies, emphasizing that restrictions must balance the morbidity and mortality attributable to the outbreak against dementia deterioration.

Even though restricted psychotropic drug use among PwD probably reflects more judicious prescribing practices in recent years, we suggest that medication reviews by GPs should be encouraged, to improve communication with patients and their

caregivers, optimize overall drug use, and increase continuity of care for this complex population. Collegial support could be exercised locally to ensure rigorous and systematic revisions [113, 129, 249, 259]

To increase the understanding of medication reviews and contextual factors' impact on BPSD, we suggest the following perspectives for future dementia research:

I. Explore medication reviews to develop sustainable integrations for decision support and collaboration in general practice and nursing homes.
II. Explore the acceptability, feasibility, and validity of technology for accurate, objective, and continuous assessment, as well as timely and remote BPSD management.
III. Investigate the independent contributions of different components in research and current practice to tailor the ideal multicomponent intervention for managing BPSD.
IV. Explore BPSD and psychotropic prescribing practices under chronic stressors, including transitions in care and the prolonged Covid-19 outbreak.

7. Errata

Paper I, Table 1: '*Formal dementia diagnosis*' should replace '*Diagnosis of demented'*. This slip was introduced by the publisher, but not detected in proofreading.

Paper I, Table 3: Instead of using the unequal variances t-test as stated, we report changes within the intervention and the control groups using the unpaired t-test. However, the results do not essentially shift on conducting the analyses using the unequal variances t-test as intended, although this mistake implies that the degrees of freedom reported are incorrect.

Paper II, Strengths and weaknesses: It is inaccurately stated that *'The parent trial population was recruited from different municipalities to be representative to the Norwegian demographic in terms of dementia aetiology, severity and symptomatology'* as the dyads in LIVE@Home.Path were recruited using non-random sampling procedures.

Paper III, Strengths and weaknesses: *"…their obligations as 'careers'"* is misspelled, should be '*carers'*.

8. References

1. The Ministry of Health and Care Services. *Medikamentfrie tilbud i psykisk helsevern - oppfølging av oppdrag 2015 [Medication-free treatment for all mentally ill patients]*, 2015. [Online] Available from: https://www.regjeringen.no/no/dokument/dep/hod/anbud-konsesjoner-og-brev/brev/utvalgte_brev/2015/medikamentfrie-tilbud-i-psykisk-helsevern---oppfolging-av-oppdrag-2015/id2464239/ [Accessed Jan 24 2022].
2. The Ministry of Health and Care Services, *Dementia plan 2020. A more dementia-friendly society.* 2016: Oslo.
3. Yeisen, R.A., et al., *Psychiatrists' reflections on a medication-free program for patients with psychosis.* J Psychopharmacol, 2019. **33**(4): p. 459-465.
4. Bednarczyk, E., et al., *Stakeholders' views on the use of psychotropic medication in older people: a systematic review.* Age Ageing, 2022. **51**(3):afac060.
5. Kales, H.C., L.N. Gitlin, and C.G. Lyketsos, *When Less is More, but Still Not Enough: Why Focusing on Limiting Antipsychotics in People With Dementia Is the Wrong Policy Imperative.* J Am Med Dir Assoc, 2019. **20**(9): p. 1074-1079.
6. Oedegaard, C.H., et al., *"It means so much for me to have a choice": a qualitative study providing first-person perspectives on medication-free treatment in mental health care.* BMC Psychiatry, 2020. **20**:399.
7. Fjermestad, T., *Ny tvangslov umyndiggjør kommunehelsetjenesten [New law on the use of coercion disempowers the municipal health service].* Tidsskr Nor Legeforen, 2022.
8. World Health Organization. *Mental health and psychosocial considerations during the COVID-19 outbreak*, 2020. [Online] Available from: https://apps.who.int/iris/handle/10665/331490 [Accessed Mar 18 2020].
9. Vahia, I.V., et al., *COVID-19, Mental Health and Aging: A Need for New Knowledge to Bridge Science and Service.* Am J Geriatr Psychiatry, 2020. **28**(7): p. 695-697.

10. Husebo, B.S. and L.I. Berge, *Intensive medicine and nursing home care in times of SARS CoV-2: a Norwegian perspective.* Am J Geriatr Psychiatry, 2020. **28**(7): p. 792-793.
11. World Health Organization. *Aging and Health*, 2021. [Online] Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [Accessed Oct 4 2021].
12. Livingston, G., et al., *Dementia prevention, intervention, and care: 2020 report of the Lancet Commission.* The Lancet, 2020. **396**(10248): p. 413-446.
13. Gjøra, L., et al., *Current and Future Prevalence Estimates of Mild Cognitive Impairment, Dementia, and Its Subtypes in a Population-Based Sample of People 70 Years and Older in Norway: The HUNT Study.* J Alzheimers Dis, 2021. **79**(3): p. 1213-1226.
14. Selbaek, G., et al., *The course of neuropsychiatric symptoms in nursing-home patients with dementia over a 53-month follow-up period.* Int Psychogeriatr, 2014. **26**(1): p. 81-91.
15. Vik-Mo, A.O., et al., *Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study.* Int J Geriatr Psychiatry, 2018. **33**(10): p. 1361-1369.
16. Daatland, S.O., K. Høyland, and B. Otnes, *Scandinavian contrasts and Norwegian variations in special housing for older people.* J Hous Elderly, 2015. **29**(1-2): p. 180-196.
17. The Ministry of Finance, *Long-term Perspectives on the Norwegian Economy 2021. Meld. St. 14 (2020–2021) Report to the Storting (white paper)*. 2021: Oslo.
18. The Ministry of Health and Care Services, *Lov om kommunale helse- og omsorgstjenester m.m. [The act on municipal healthcare services]* 2011: Oslo.
19. Selbæk, G., K. Engedal, and S. Bergh, *The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review.* J Am Med Dir Assoc, 2013. **14**(3): p. 161-169.
20. Sanford, A.M., et al., *An international definition for "nursing home".* J Am Med Dir Assoc, 2015. **16**(3): p. 181-184.

21. World Health Organization. *Dementia fact sheet,* 2021. [Online] Available from: https://www.who.int/news-room/fact-sheets/detail/dementia [Accessed Jan 18 2022].
22. Lamberts, H., M. Wood, and I. Hofmans-Okkes, *The International classification of primary care in the European community: with a multi-language layer*. 1993: Oxford university press.
23. World Health Organization, *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. 1992, Geneva World Health Organization.
24. The Norwegian National Centre for Ageing and Health. *Basal demensutredning [Basic dementia evaluation],* 2017. [Online] Available from: https://www.aldringoghelse.no/demens/utredning-av-demens/basal-demensutredning/ [Accessed May 22 2019].
25. Directorate of Health. *Nasjonal faglig retningslinje for demens [National professional guidelines on dementia],* 2020. [Online] Available from: https://www.helsedirektoratet.no/retningslinjer/demens [Accessed Mar 8 2020].
26. Directorate of Health, *Nasjonal kartlegging av kommunenes tilrettelagte tjenestetilbud til personer med demens 2018 [Municipal health care services for people with dementia in Norway 2018]*. 2019, Directorate of Health: Oslo.
27. Ryan, B., et al., *Sociodemographic and Clinical Characteristics of 1350 Patients With Young Onset Dementia: A Comparison With Older Patients.* Alzheimer Dis Assoc Disord, 2021. **35**(3): p. 200-207.
28. Cummings, J., *The Role of Neuropsychiatric Symptoms in Research Diagnostic Criteria for Neurodegenerative Diseases.* Am J Geriatr Psychiatry, 2021. **29**(4): p. 375-383.
29. Goodman, R.A., et al., *Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011–2013.* Alzheimers Dement, 2017. **13**(1): p. 28-37.

30. Jones, S.V. and J. O'Brien, *The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies.* Psychol Med, 2014. **44**(4): p. 673-683.
31. Bränsvik, V., et al., *Mortality in patients with behavioural and psychological symptoms of dementia: a registry-based study.* Aging Ment Health, 2021. **25**(6): p. 1101-1109.
32. Knopman, D.S., et al., *Alzheimer disease.* Nat Rev Dis Primers, 2021. **7**(1): p. 33.
33. McKeith, I.G., et al., *Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium.* Neurology, 2017. **89**(1): p. 88-100.
34. Bir, S.C., et al., *Emerging Concepts in Vascular Dementia: a Review.* J Stroke Cerebrovasc Dis, 2021. **30**(8):105864.
35. Fierini, F., *Mixed dementia: Neglected clinical entity or nosographic artifice?* J Neurol Sci, 2020. **410**:116662.
36. Vossius, C., et al., *Ressursbruk og sykdomsforløp ved demens (REDIC): langversjon [Resource utilization and symptom progression in dementia (REDIC): extended version]*. 2015, Alderspsykiatrisk forskningssenter, Sykehuset Innlandet HF, Helse Sør-Øst: Ottestad.
37. Helvik, A.-S., et al., *Prevalence and Severity of Dementia in Nursing Home Residents.* Dement Geriatr Cogn Disord, 2015. **40**(3-4): p. 166-177.
38. Wergeland, J.N., et al., *Dementia, neuropsychiatric symptoms, and the use of psychotropic drugs among older people who receive domiciliary care: a cross-sectional study.* Int Psychogeriatr, 2014. **26**(3): p. 383-391.
39. Reisberg, B., *Functional assessment staging (FAST).* Psychopharmacol Bull, 1988. **24**(4): p. 653-659.
40. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *Mini-Mental State - Practical Method for Grading Cognitive State of Patients for Clinician.* J Psychiatr Res, 1975. **12**(3): p. 189-198.

41. Jorm, A., *A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation.* Psychological medicine, 1994. **24**(1): p. 145-153.
42. Hughes, C.P., et al., *A new clinical scale for the staging of dementia.* The British journal of psychiatry, 1982. **140**(6): p. 566-572.
43. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment.* J Am Geriatr Soc, 2005. **53**(4): p. 695-699.
44. Shulman, K.I., R. Shedletsky, and I.L. Silver, *The challenge of time: clock-drawing and cognitive function in the elderly.* Int J Geriatr Psychiatry, 1986. **1**(2): p. 135-140.
45. Wolf-Klein, G.P., et al., *Screening for Alzheimer's disease by clock drawing.* J Am Geriatr Soc, 1989. **37**(8): p. 730-734.
46. Finkel, S.I., et al., *Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment.* Int Psychogeriatr, 1997. **8**(S3): p. 497-500.
47. Assal, F., *History of Dementia* in *A History of Neuropsychology*, Bogousslavsky J, F. Boller, and I. M, Editors. 2019, Front Neurol Neurosci: Basel, Switzerland. p. 118-126.
48. Merriam-Webster, *Dementia*, in *Merriam-Webster*. n.d., Merriam-Webster.
49. Alzheimer, A., et al., *An English translation of Alzheimer's 1907 paper,"Uber eine eigenartige Erkankung der Hirnrinde".* Clinical Anatomy, 1995. **8**(6): p. 429-431.
50. van der Linde, R.M., et al., *Grouping of behavioural and psychological symptoms of dementia.* Int J Geriatr Psychiatry, 2014. **29**(6): p. 562-568.
51. Aalten, P., et al., *Behavioral problems in dementia: A factor analysis of the neuropsychiatric inventory.* Dement Geriatr Cogn Disord, 2003. **15**(2): p. 99-105.
52. van der Linde, R.M., et al., *Longitudinal course of behavioural and psychological symptoms of dementia: systematic review.* Br J Psychiatry, 2016. **209**(5): p. 366-377.

53. Vik-Mo, A.O., et al., *The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study.* Br J Psychiatry, 2020. **216**(1): p. 43-48.
54. Cummings, J., *The Neuropsychiatric Inventory: Development and Applications.* J Geriatr Psychiatry Neurol, 2020. **33**(2): p. 73-84.
55. Watt, J.A., et al., *Managing neuropsychiatric symptoms in patients with dementia.* BMJ, 2022. **376**:069187.
56. Alexopoulos, G.S., et al., *Cornell Scale for Depression in Dementia.* Biol Psychiatry, 1988. **23**(3): p. 271-284.
57. Cohen-Mansfield, J. and A. Libin, *Assessment of agitation in elderly patients with dementia: correlations between informant rating and direct observation.* Int J Geriatr Psychiatry, 2004. **19**(9): p. 881-891.
58. Lyketsos, C., *Neuropsychiatric Symptoms in Dementia: Overview and Measurement Challenges.* J Prev Alzheimers Dis, 2015. **2**(3): p. 155-156.
59. Ballard, C.G., et al., *Management of agitation and aggression associated with Alzheimer disease.* Nat Rev Neurol, 2009. **5**(5): p. 245-255.
60. Esteban de Antonio, E., et al., *Pathological Correlations of Neuropsychiatric Symptoms in Institutionalized People with Dementia.* J Alzheimer's Dis, 2020. **78**(4): p. 1731-1741.
61. Cummings, J., *New approaches to symptomatic treatments for Alzheimer's disease.* Mol Neurodegener, 2021. **16**(1): p. 2.
62. Jeste, D.V., et al., *ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia.* Neuropsychopharmacology, 2008. **33**(5): p. 957-970.
63. Devanand, D.P., et al., *Associations Between Neuropsychiatric Symptoms and Neuropathological Diagnoses of Alzheimer Disease and Related Dementias.* JAMA Psychiatry, 2022. **79**(4): p. 359-367.
64. Tampi, R.R. and D.V. Jeste, *Dementia Is More Than Memory Loss: Neuropsychiatric Symptoms of Dementia and Their Nonpharmacological and Pharmacological Management.* Am J Psychiatry, 2022. **179**(8): p. 528-543.

65. Livingston, G., et al., *A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia.* Health Technol Assess, 2014. **18**(39): p. 1-226.

66. Ingram, R.E. and D.D. Luxton, *Vulnerability-Stress models*, ed. B.L. Hankin and J.R.Z. Abela. 2005, Thousand Oaks, Canada: SAGE Publications Ltd.

67. American Psychiatric Association, *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013.

68. Fong, T.G., et al., *The interface between delirium and dementia in elderly adults.* Lancet Neurol, 2015. **14**(8): p. 823-832.

69. Pisani, M. *Assessment of delirium*, 2021. [Online] Available from: https://bestpractice.bmj.com/topics/en-gb/241. [Accessed May 10 2022].

70. Directorate of Health. *Nasjonale faglige råd - Delirium [National advice on delirium]*, 2019. [Online] Available from: https://www.helsedirektoratet.no/faglige-rad/psykiske-lidelser-hos-eldre/delirium [Accessed May 10 2022].

71. Kales, H.C., et al., *Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus.* Int Psychogeriatr, 2019. **31**(1): p. 83-90.

72. Watt, J.A., et al., *Comparative efficacy of interventions for reducing symptoms of depression in people with dementia: systematic review and network meta-analysis.* BMJ, 2021. **372**:n532.

73. Watt, J.A., et al., *Comparative Efficacy of Interventions for Aggressive and Agitated Behaviors in Dementia: A Systematic Review and Network Meta-analysis.* Ann Intern Med, 2019. **171**(9): p. 633-642.

74. Kales, H.C., L.N. Gitlin, and C.G. Lyketsos, *Assessment and management of behavioral and psychological symptoms of dementia.* BMJ, 2015. **350**:h369.

75. Lichtwarck, B., et al., *Targeted interdisciplinary model for evaluation and treatment of neuropsychiatric symptoms: a cluster randomized controlled trial.* am J Geriatr Psychiatry, 2018. **26**(1): p. 25-38.

76. Gallacher, J. and A. Burns, *Social prescribing in dementia.* Lancet Neurol, 2021. **20**(9): p. 707-708.

77. Bessey, L.J. and A. Walaszek, *Management of Behavioral and Psychological Symptoms of Dementia.* Curr Psychiatry Rep, 2019. **21**(8):66.

78. WHO collaborating Centre for Drug Statistics Methodology, *ATC/DDD index [database online]*. 2015, Norwegian Institute of Public Health: Oslo.

79. Magierski, R., et al., *Pharmacotherapy of Behavioral and Psychological Symptoms of Dementia: State of the Art and Future Progress.* Front Pharmacol, 2020. **11**(31):1168.

80. Tampi, R.R., et al., *Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses.* Ther Adv Chronic Dis, 2016. **7**(5): p. 229-245.

81. Mühlbauer, V., et al., *Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia.* Cochrane Database Syst Rev, 2021. **12**(12):CD013304.

82. Hsu, T.-W., et al., *Efficacy of serotonergic antidepressant treatment for the neuropsychiatric symptoms and agitation in dementia: A systematic review and meta-analysis.* Ageing Res Rev, 2021. **69**:101362.

83. Dudas, R., et al., *Antidepressants for treating depression in dementia.* Cochrane Database Syst Rev, 2018. **31**(8):CD003944.

84. Richardson, K., et al., *Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study.* BMC Med, 2020. **18**(1):351.

85. McCleery, J., D.A. Cohen, and A.L. Sharpley, *Pharmacotherapies for sleep disturbances in dementia.* Cochrane Database Syst Rev, 2020. **11**(11):CD009178.

86. Tsoi, K.K., et al., *Monotherapy Is Good Enough for Patients with Mild-to-Moderate Alzheimer's Disease: A Network Meta-analysis of 76 Randomized Controlled Trials.* Clin Pharmacol Ther, 2019. **105**(1): p. 121-130.

87. Dou, K.-X., et al., *Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials.* Alzheimers Res Ther, 2018. **10**(1):126.
88. Suzuki, Y., et al., *Use of Anti-Dementia Drugs Reduces the Risk of Potentially Inappropriate Medications: A Secondary Analysis of a Nationwide Survey of Prescribing Pharmacies.* Dement Geriatr Cogn Disord, 2020. **49**(5): p. 526-532.
89. Janus, S.I., et al., *Psychotropic drug prescriptions in Western European nursing homes.* Int Psychogeriatr, 2016. **28**(11): p. 1775-1790.
90. Jester, D.J., et al., *Prevalence of psychotropic polypharmacy in nursing home residents with dementia: a meta-analysis.* Int Psychogeriatr, 2021. **33**(10): p. 1083-1098.
91. Tran, C.T., et al., *Antipsychotic treatment patterns in Alzheimer's disease patients with agitation: a cohort study using the UK clinical practice research datalink.* Curr Med Res Opin, 2022. **38**(3): p. 409-416.
92. Borsje, P., et al., *Neuropsychiatric symptoms and psychotropic drug use in patients with dementia in general practices.* Fam Pract, 2017. **35**(1): p. 22-28.
93. Oesterhus, R., et al., *Potentially inappropriate medications and drug–drug interactions in home-dwelling people with mild dementia.* Int J Geriatr Psychiatry, 2017. **32**(2): p. 183-192.
94. Callegari, E., et al., *Does Psychotropic Drug Prescription Change in Nursing Home Patients the First 6 months After Admission?* J Am Med Dir Assoc, 2021. **22**(1): p. 101-108.
95. Fog, A.F., et al., *Variation between nursing homes in drug use and in drug-related problems.* BMC Geriatr, 2020. **20**:336.
96. World Health Organization, *Medication Safety in Polypharmacy*. 2019, World Health Organization: Geneva.
97. Belfrage, B., et al., *Number of drugs in the medication list as an indicator of prescribing quality: a validation study of polypharmacy indicators in older hip fracture patients.* Eur J Clin Pharmacol, 2015. **71**(3): p. 363-368.

98. Lombardi, F., et al., *Underprescription of medications in older adults: causes, consequences and solutions—a narrative review.* Eur Geriatr Med, 2021. **12**(3): p. 453-462.

99. Drenth-van Maanen, A.C., I. Wilting, and P.A. Jansen, *Prescribing medicines to older people—How to consider the impact of ageing on human organ and body functions.* British Journal of Clinical Pharmacology, 2020. **86**(10): p. 1921-1930.

100. McGrattan, M., et al., *Interventions to improve medicines management for people with dementia: a systematic review.* Drugs Aging, 2017. **34**(12): p. 907-916.

101. Ruths, S., et al., *Trends in psychotropic drug prescribing in Norwegian nursing homes from 1997 to 2009: a comparison of six cohorts.* Int J Geriatr Psychiatry, 2013. **28**(8): p. 868-876.

102. Selbaek, G., et al., *Change in psychotropic drug use in Norwegian nursing homes between 2004 and 2011.* Int Psychogeriatr, 2018. **30**(3): p. 385-394.

103. Donegan, K., et al., *Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study.* Lancet Public Health, 2017. **2**(3): p. e149-e156.

104. Du, J., et al., *Time trends in psychotropic drug prescriptions in Dutch nursing home residents with dementia between 2003 and 2018.* Int J Geriatr Psychiatry, 2022. **37**(4): p. 1-10.

105. Gulla, C., 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.

106. Ito, E., et al., *The Negative Impact of Psychotropic Drug Use on Quality of Life in Nursing Home Patients at Different Stages of Dementia: Cross-Sectional Analyses from the COSMOS Trial.* J Am Med Dir Assoc, 2020. **21**(11): p. 1623-1628.

107. Spinewine, A., et al., *Appropriate prescribing in elderly people: how well can it be measured and optimised?* Lancet, 2007. **370**(9582): p. 173-184.

108. Curtin, D., P.F. Gallagher, and D. O'Mahony, *Explicit criteria as clinical tools to minimize inappropriate medication use and its consequences.* Ther Adv Drug Saf, 2019. **10**: p. 1-10.

109. Hukins, D., U. Macleod, and J.W. Boland, *Identifying potentially inappropriate prescribing in older people with dementia: a systematic review.* Eur J Clin Pharmacol, 2019. **75**(4): p. 467-481.

110. van der Spek, K., et al., *The effect of biannual medication reviews on the appropriateness of psychotropic drug use for neuropsychiatric symptoms in patients with dementia: a randomised controlled trial.* Age Ageing, 2018. **47**(3): p. 430-437.

111. Samsa, G.P., et al., *A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity.* J Clin Epidemiol, 1994. **47**(8): p. 891-896.

112. Wang-Hansen, M.S., et al., *Can screening tools for potentially inappropriate prescriptions in older adults prevent serious adverse drug events?* Eur J Clin Pharmacol, 2019. **75**(5): p. 627-637.

113. Rognstad, S., et al., *Prescription peer academic detailing to reduce inappropriate prescribing for older patients: a cluster randomised controlled trial.* Br J Gen Pract, 2013. **63**(613):e554-e562.

114. American Geriatrics Society Beers Criteria® Update Expert Panel, et al., *American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults.* J Am Geriatr Soc, 2019. **67**(4): p. 674-694.

115. Rognstad, S., et al., *The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients: a modified Delphi study.* Scand J Prim Health Care, 2009. **27**(3): p. 153-159.

116. Nyborg, G., et al., *The Norwegian General Practice – Nursing Home criteria (NORGEP-NH) for potentially inappropriate medication use: A web-based Delphi study.* Scand J Prim Health Care, 2015. **33**(2): p. 134-141.

117. Holt, S., S. Schmiedl, and P.A. Thürmann, *Potentially inappropriate medications in the elderly: the PRISCUS list.* Dtsch Arztebl Int, 2010. **107**(31-32): p. 543-551.
118. O'Mahony, D., et al., *STOPP/START criteria for potentially inappropriate prescribing in older people: version 2.* Age Ageing, 2015. **44**: p. 213-218.
119. Pazan, F., et al., *The FORTA (Fit fOR The Aged) List 2015: Update of a Validated Clinical Tool for Improved Pharmacotherapy in the Elderly.* Drugs Aging, 2016. **33**(6): p. 447-449.
120. Griese-Mammen, N., et al., *PCNE definition of medication review: reaching agreement.* Int J Clin Pharm, 2018. **40**(5): p. 1199-1208.
121. Reeve, E., et al., *A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice.* Br J Clin Pharmacol, 2015. **80**(6): p. 1254-1268.
122. Granås, A.G., et al., *Deprescribing.* Tidsskr Nor Legeforen, 2018. **138**(4).
123. Scott, I.A., et al., *Reducing inappropriate polypharmacy: the process of deprescribing.* JAMA Intern Med, 2015. **175**(5): p. 827-834.
124. Sawan, M.J., et al., *The value of deprescribing in older adults with dementia: a narrative review.* Expert Rev Clin Pharmacol, 2021. **14**(11): p. 1367-1382.
125. The Ministry of Health and Care Services, *Forskrift om fastlegeordning i kommunene [Act on the regular general practitioner scheme in the municipalities]*. 2012.
126. The Ministry of Health and Care Services, *Forskrift om legemiddelhåndtering for virksomheter og helsepersonell som yter helsehjelp [Act on medication administration in institutions and for health care personnel who provide health care]*. 2008.
127. Hermann, M., et al., *Medication reviews on admission of residents to nursing homes.* Norwegian Journal of Clinical Nursing/Sykepleien Forskning, 2021. **16**:e-86715.
128. Husebo, B.S., 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.

129. Gulla, C., et al., *Implementing a novel strategy for interprofessional medication review using collegial mentoring and systematic clinical evaluation in nursing homes (COSMOS).* BMC Geriatr, 2019. **19**:130.
130. Husebo, B.S., et al., *The Effect of a Multicomponent Intervention on Quality of Life in Residents of Nursing Homes: A Randomized Controlled Trial (COSMOS).* J Am Med Dir Assoc, 2019. **20**: p. 330-339.
131. Gulla, C., et al., *Deprescribing antihypertensive treatment in nursing home patients and the effect on blood pressure.* J Geriatr Cardiol, 2018. **15**(4): p. 275-283.
132. Flo-Groeneboom, E., et al., *The longitudinal association between the use of antihypertensive medications and 24-hour sleep in nursing homes: results from the randomized controlled COSMOS trial.* BMC Geriatr, 2021. **21**:430.
133. Aasmul, I., et al., *Advance Care Planning in Nursing Homes – Improving the Communication Among Patient, Family, and Staff: Results From a Cluster Randomized Controlled Trial (COSMOS).* Front Psychol, 2018. **9**:2284.
134. Wiggin, D.A., et al., *Improving the appropriateness of psychotropic prescribing for nursing home residents with dementia: an overview of reviews.* Aging Ment Health, 2022. **26**(6): p. 1087-1094.
135. Moth, A.E., et al., *What Makes Deprescription of psychotropic drugs in nursing home residents with dementia so challenging? A qualitative systematic review of barriers and facilitators.* Drugs Aging, 2021. **38**(8): p. 671-685.
136. Skivington, K., et al., *A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance.* BMJ, 2021. **374**:n2061.
137. Clark, A.M., *What are the components of complex interventions in healthcare? Theorizing approaches to parts, powers and the whole intervention.* Soc Sci Med, 2013. **93**: p. 185-193.
138. Petticrew, M., *When are complex interventions 'complex'? When are simple interventions 'simple'?* Eur J Public Health, 2011. **21**(4): p. 397-398.

139. Özbe, D., et al., *Immediate Intervention Effects of Standardized Multicomponent Group Interventions on People with Cognitive Impairment: a Systematic Review.* J Alzheimers Dis, 2019. **67**(2): p. 653-670.
140. Guise, J.-M., et al., *Systematic Reviews of Complex Multicomponent Health Care Interventions [Internet]*. 2014: Rockville, Maryland, US.
141. Coon, J.T., et al., *Interventions to Reduce Inappropriate Prescribing of Antipsychotic Medications in People with Dementia Resident in Care Homes: A Systematic Review.* J Am Med Dir Assoc, 2014. **15**(10): p. 706-718.
142. Ballard, C., et al., *Impact of Antipsychotic Review and Nonpharmacological Intervention on Antipsychotic Use, Neuropsychiatric Symptoms, and Mortality in People with Dementia Living in Nursing Homes: A Factorial Cluster-Randomized Controlled Trial by the Well-Being and Health for People with Dementia (WHELD) Program.* Am J Psychiatry, 2016. **173**(3): p. 252-262.
143. Cossette, B., et al., *Optimizing Practices, Use, Care and Services–Antipsychotics (OPUS-AP) in Long-term Care Centers in Québec, Canada: A Strategy for Best Practices.* J Am Med Dir Assoc, 2020. **21**(2): p. 212-219.
144. Fossey, J., et al., *Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial.* BMJ, 2006. **332**(7544): p. 756-761.
145. Mesquida, M.M., et al., *Consensus and evidence-based medication review to optimize and potentially reduce psychotropic drug prescription in institutionalized dementia patients.* BMC Geriatr, 2019. **19**:7.
146. Westbury, J.L., et al., *RedUSe: reducing antipsychotic and benzodiazepine prescribing in residential aged care facilities.* Med J Aust, 2018. **208**(9): p. 398-403.
147. Hoyle, D.J., et al., *Clinical impact of antipsychotic and benzodiazepine reduction: findings from a multicomponent psychotropic reduction program within long-term aged care.* Int Psychogeriatr, 2021. **33**(6): p. 587-599.
148. Almutairi, H., et al., *Optimisation of medications used in residential aged care facilities: a systematic review and meta-analysis of randomised controlled trials.* BMC Geriatr, 2020. **20**:236.

149. Torres-Castro, S., et al., *Multicomponent Staff Training Intervention to Improve Residential Dementia Care (PROCUIDA-Demencia): A Mixed-Methods 2-Arm Cluster Randomized Controlled Pilot and Clinical Outcomes Study.* J Am Med Dir Assoc, 2022. **23**(3):350-358.e5.

150. Maidment, I.D., et al., *Medication review plus person-centred care: a feasibility study of a pharmacy-health psychology dual intervention to improve care for people living with dementia.* BMC Psychiatry, 2018. **18**:340.

151. Nunez, K. *Reducing Hypnotic Drug Use and Improving Night-time Care for People Living With Dementia in Care Homes (NightCAP): A Randomised Factorial Trial,* 2022. [Online] Available from: https://clinicaltrials.gov/ct2/show/study/NCT04373668 [Accessed Sept 9 2022].

152. Thyrian, J.R. *Implementing Dementia Care Management Into Routine Care in the Region Siegen-Wittgenstein (RoutineDeCM),* 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05529277. [Accessed Sept 9 2022].

153. Fortinsky, R. *3D Team Care for Cognitively Vulnerable Older Adults*, 2022. [Online] Available from: https://clinicaltrials.gov/ct2/show/NCT02945085 [Accessed Sept 9 2022].

154. Spieth, P.M., et al., *Randomized controlled trials–a matter of design.* Neuropsychiatr Dis Treat, 2016. **12**: p. 1341-1349.

155. Bauer, M.S. and J. Kirchner, *Implementation science: What is it and why should I care?* Psychiatry Res, 2020. **283**:112376.

156. Proctor, E., et al., *Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda.* Adm Policy Ment Health, 2011. **38**(2): p. 65-76.

157. Landes, S.J., S.A. McBain, and G.M. Curran, *Reprint of: an introduction to effectiveness-implementation hybrid designs.* Psychiatry Res, 2020. **283**:112630.

158. The Office of the Prime Minister. *Long-term strategy and plan for handling the Covid-19 pandemic and adjustment of measures,* 2020. [Online] Available from: https://www.regjeringen.no/en/dokumenter/long-term-strategy-and-plan-

for-handling-the-covid-19-pandemic-and-adjustment-of-measures/id2701518/ [Accessed June 9 2020].

159. Andersen, K.G.R., Andrew, et al., *The proximal origin of SARS-CoV-2.* Nat Med, 2020. **26**: p. 450-452.

160. Norwegian Institute of Public Health. *Facts about the SARS-CoV-2 virus and COVID-19 disease*, 2020. [Online] Available from: https://www.fhi.no/en/op/novel-coronavirus-facts-advice/facts-and-knowledge-about-covid-19/facts-about-novel-coronavirus/ [Accessed Jan 16 2022].

161. Norwegian Government Security and Service Organisation. *Timeline: News from Norwegian Ministries about the Coronavirus disease Covid-19*, 2022. [Online] Available from: https://www.regjeringen.no/en/topics/koronavirus-covid-19/timeline-for-news-from-norwegian-ministries-about-the-coronavirus-disease-covid-19/id2692402/ [Accessed Sept 6 2022].

162. World Health Organization. *WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020,* 2020. [Online] Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020#:~:text=WHO%20has%20been%20assessing%20this,to%20use%20lightly%20or%20carelessly [Accessed Jan 16 2022].

163. Samadizadeh, S., et al., *COVID-19: Why does disease severity vary among individuals?* Respir Med, 2021. **180**:106356.

164. Saragih, I.D., et al., *Dementia as a mortality predictor among older adults with COVID-19: A systematic review and meta-analysis of observational study.* Geriatr Nurs, 2021. **42**(5): p. 1230-1239.

165. Cray, H.V. and I.V. Vahia, *Two Years of COVID-19: Understanding Impact and Implications for the Mental Health of Older Adults.* Am J Geriatr Psychiatry, 2022. **30**(4): p. 444-447.

166. Husebo, B.S., et al., *LIVE@Home.Path —innovating the clinical pathway for home-dwelling people with dementia and their caregivers: study protocol for a*

mixed-method, stepped-wedge, randomized controlled trial. Trials, 2020. **21**:510.

167. Gedde, M.H., et al., *Access to and interest in assistive technology for home-dwelling people with dementia during the COVID-19 pandemic (PAN.DEM).* Int Rev Psychiatry, 2021. **33**(4): p. 404-411.
168. Giebel, C., et al., *COVID-19-related social support service closures and mental well-being in older adults and those affected by dementia: a UK longitudinal survey.* BMJ Open, 2021. **11**(1):e045889.
169. Lara, B.B., et al., *Neuropsychiatric symptoms and quality of life in Spanish Alzheimer's disease patients during COVID-19 lockdown.* Eur J Neurol, 2020. **27**(9): p. 1744-1747.
170. Moretti, R., et al. *COVID-19 Lockdown Effect on Not Institutionalized Patients with Dementia and Caregivers*. Healthcare, 2021. **9**:893.
171. Sizoo, E.M., et al., *The course of neuropsychiatric symptoms and psychotropic drug use in Dutch nursing home patients with dementia during the first wave of COVID-19: A longitudinal cohort study.* Int J Geriatr Psychiatry, 2022. **37**: p. 1-9.
172. Vernuccio, L., et al., *Effect of COVID-19 quarantine on cognitive, functional and neuropsychiatric symptoms in patients with mild cognitive impairment and dementia.* Aging Clin Exp Res, 2022. **34**(5): p. 1187-1194.
173. Husebo, B.S., R. Ostelo, and L.I. Strand, *The MOBID-2 pain scale: Reliability and responsiveness to pain in patients with dementia.* Eur J Pain, 2014. **18**(10): p. 1419-1430.
174. Norwegian Medicines Agency, *Interaksjoner.no [database online]*. 2014, Norwegian Medicines Agency: Bergen.
175. Norwegian Medicines Agency. *Sjekkliste for legemiddelgjennomgang [Check list for medication review]*, 2016. [Online] Available from: https://www.helsebiblioteket.no/251793.cms [Accessed Oct 10 2019].
176. Duran, C.E., M. Azermai, and R.H. Vander Stichele, *Systematic review of anticholinergic risk scales in older adults.* Eur J Clin Pharmacol, 2013. **69**(7): p. 1485-1496.

177. Fæø, S.E., et al., *The compound role of a coordinator for home-dwelling persons with dementia and their informal caregivers: qualitative study.* BMC Health Serv Res, 2020. **20**:1045.

178. Puaschitz, N.G., et al., *Factors associated with access to assistive technology and telecare in home-dwelling people with dementia: baseline data from the LIVE@Home.Path trial.* BMC Med Inform Decis Mak, 2021. **21**:264.

179. Berge, L.I., et al., *The acceptability, adoption, and feasibility of a music application developed using participatory design for home-dwelling persons with dementia and their caregivers. The "Alight" app in the LIVE@Home.Path trial.* Front Psychiatry, 2022. **13**:949393.

180. Wilcox, A.B., K. Gallagher, and S. Bakken, *Security approaches in using tablet computers for primary data collection in clinical research.* EGEMS (Wash DC), 2013. **1**(1):1008.

181. Devsoft Baltic OÜ. *SurveyJS*, 2020. [Online] Available from: https://surveyjs.io/ [Accessed Feb 10 2020].

182. Lawton, M.P. and E.M. Brody, *Assessment of older people: self-maintaining and instrumental activities of daily living.* Gerontologist, 1969. **9**(3): p. 179-186.

183. Lyketsos, C.G., et al., *The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia.* J Am Geriatr Soc, 1999. **47**(4): p. 487-491.

184. Guy, W., *ECDEU assessment manual for psychopharmacology*. 1976, Rockville, MD, US: US Department of Health, Education and Welfare.

185. Perneczky, R., et al., *Mapping scores onto stages: mini-mental state examination and clinical dementia rating.* Am J Geriatr Psychiatry, 2006. **14**(2): p. 139-144.

186. Sclan, S.G. and B. Reisberg, *Functional assessment staging (FAST) in Alzheimer's disease: reliability, validity, and ordinality.* Int Psychogeriatr, 1992. **4**: p. 55-69.

187. Lyketsos, C.G., *Neuropsychiatric symptoms (behavioral and psychological symptoms of dementia) and the development of dementia treatments.* Int Psychogeriatr, 2007. **19**(3): p. 409-420.
188. Selbaek, G., et al., *The reliability and validity of the Norwegian version of the neuropsychiatric inventory, nursing home version (NPI-NH).* Int Psychogeriatr, 2008. **20**(2): p. 375-382.
189. Barca, M.L., K. Engedal, and G. Selbæk, *A Reliability and Validity Study of the Cornell Scale among Elderly Inpatients, Using Various Clinical Criteria. .* Dement Geriatr Cogn Disord, 2010. **29**(5): p. 438-447.
190. The Ministry of Health and Care Services, *Lov om medisinsk og helsefaglig forskning [The Health Research Act]*. 2008: Oslo.
191. Directorate of eHealth. *Implementation of GDPR in health care sector in Norway,* 2019. [Online] Available from: https://www.ehelse.no/personvern-og-informasjonssikkerhet/implementation-of-gdpr-in-health-care-sector-in-norway [Accessed Nov 9 2021].
192. The Ministry of Justice and Public Security, *Lov om behandling av personopplysninger [Personal data act]* 2018: Oslo.
193. World Health Organization, *Towards a dementia plan: a WHO guide*. 2018, World Health Organization: Geneva.
194. Schuijff, M. and A.M. Dijkstra, *Practices of Responsible Research and Innovation: A Review.* Sci Eng Ethics, 2020. **26**(2): p. 533-574.
195. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* BMJ, 2011. **343**:d5928.
196. Catalogue of Bias Collaboration, et al. *Selection bias*, 2017. [Online] Available from: http://www.catalogofbias.org/biases/selection-bias/ [Accessed July 4 2022].
197. Kahan, B.C., S. Rehal, and S. Cro, *Risk of selection bias in randomised trials.* Trials, 2015. **16**:405.
198. Hemming, K., et al., *The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting.* BMJ, 2015. **350**:h391.

199. Catalogue of Bias Collaboration, et al. *Detection bias*, 2017. [Online] Available from: https://catalogofbias.org/biases/detection-bias/ [Accessed July 4 2022].

200. Bergh, S., G. Selbæk, and K. Engedal, *Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial.* BMJ, 2012. **344**:e1566.

201. Catalogue of Bias Collaboration, et al. *Performance bias*, 2019. [Online] Available from: https://catalogofbias.org/biases/performance-bias/s [Accessed July 4 2022].

202. Eldridge, S., et al., *Internal and external validity of cluster randomised trials: systematic review of recent trials.* BMJ, 2008. **336**(7649): p. 876-880.

203. Catalogue of Bias Collaboration, E. Spencer, and K. Mahtani. *Hawthorne effect,* 2017. [Online] Available from: https://catalogofbias.org/biases/hawthorne-effect/ [Accessed July 6 2022].

204. Catalogue of Bias Collaboration, et al. *Attrition bias*, 2017. [Online] Available from: https://catalogofbias.org/biases/attrition-bias/ [Accessed July 4 2022].

205. Catalogue of Bias Collaboration, G. Richards, and I. Onakpoya. *Reporting biases*, 2019. [Online] Available from: https://catalogofbias.org/biases/reporting-biases/ [Accessed July 4 2022].

206. Rothwell, P.M., *External validity of randomised controlled trials:"to whom do the results of this trial apply?".* Lancet, 2005. **365**(9453): p. 82-93.

207. Kennedy-Martin, T., et al., *A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results.* Trials, 2015. **16**(3):495.

208. Selbæk, G., Ø. Kirkevold, and K. Engedal, *The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes.* Int J Geriatr Psychiatry, 2007. **22**(9): p. 843-849.

209. The Norwegian National Centre for Ageing and Health. *The Norwegian registry of persons assessed for cognitive symptoms (NorCog),* 2021. [Online]

Available from: https://www.aldringoghelse.no/forskning/norkog/information-in-english/ [Accessed July 22 2022].

210. Directorate of Health. *KUHR-databasen [The KUHR database]*, 2019. [Online] Available from: https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/kuhr [Accessed July 22 2022].
211. Kristoffersen, E.S., et al., *The Norwegian PraksisNett: a nationwide practice-based research network with a novel IT infrastructure.* Scand J Prim Health Care, 2022. **40**(2): p. 217-226.
212. Lesko, C.R., et al., *Target validity: Bringing treatment of external validitiy in line with internal validity.* Curr Epidemiol Rep, 2020. **7**(3): p. 117-124.
213. Lyngbakken, M.N., et al., *Pragmatic trials - what are they?* Tidsskr Nor Legeforen., 2021.
214. The Ministry of Health and Care Services. *Pasientsikkerhetsprogrammet; medikamentgjennomgang i sykehjem [The Norwegian Patient Safety Programme; Medication review in nursing homes]*, 2014. [Online] Available from: http://www.pasientsikkerhetsprogrammet.no/om-oss/innsatsomr%C3%A5der/riktig-legemiddelbruk-i-sykehjem [cited October 10 2019].
215. Borsje, P., et al., *The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review.* Int Psychogeriatr, 2015. **27**(3): p. 385-405.
216. Geda, Y.E., et al., *Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future.* Alzheimers Dement, 2013. **9**(5): p. 602-608.
217. Wongpakaran, N., T. Wongpakaran, and R. Van Reekum, *Discrepancies in Cornell Scale for Depression in Dementia (CSDD) items between residents and caregivers, and the CSDD's factor structure.* Clin Interv Aging, 2013. **8**: p. 641-648.
218. Blytt, K.M., et al., *Clinically significant discrepancies between sleep problems assessed by standard clinical tools and actigraphy.* BMC Geriatr, 2017. **17**:253.

219. Husebo, B.S., et al., *Sensing Technology to Monitor Behavioral and Psychological Symptoms and to Assess Treatment Response in People With Dementia. A Systematic Review.* Front Pharmacol, 2020. **10**:1699.

220. Jeon, Y.-H., et al., *Recommended measures for the assessment of behavioral disturbances associated with dementia.* Am J Geriatr Psychiatry, 2011. **19**(5): p. 403-415.

221. Habiger, T.F., et al., *Psychosis symptoms in nursing home residents with and without dementia – Cross-sectional analyses from the COSMOS study.* Int J Geriatr Psychiatry, 2019. **34**(5): p. 683-691.

222. Wilson, S., *Naming the drugs we use: neuroscience-based nomenclature, a helpful innovation.* Ther Adv Psychopharmacol, 2018. **8**(6): p. 171-172.

223. European College of Neuropsychopharmacology. *NbN: New knowledge, New Nomenclature*, 2017. [Online] Available from: https://nbn2r.com/ [Accessed Dec 20 2019].

224. Gedde, M.H., Husebo, B.S., Berge, L.I., *P.0441 Multicomponent intervention with medication reviews impact on psychotropic drug use and behavioural and psychological symptoms in home-dwelling persons with dementia*, in *The European College of Neuropsychopharmacology Congress 2021*. 2021: Virtual.

225. Gedde, M.H., Husebo, B.S., Berge, L.I., *Deprescribing of psychotropic drugs on behavioural and psychological symptoms of dementia and activities of daily living in nursing homes.*, in *The European College of Neuropsychopharmacology Congress 2020*. 2020: Virtual.

226. Herbert, E., S.A. Julious, and S. Goodacre, *Progression criteria in trials with an internal pilot: an audit of publicly funded randomised controlled trials.* Trials, 2019. **20**:493.

227. Avery, K.N., et al., *Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies.* BMJ Open, 2017. **7**(2):e013537.

228. Mettert, K., et al., *Measuring implementation outcomes: An updated systematic review of measures' psychometric properties.* Implementation Research and Practice, 2020. **1**: p. 1-29.

229. Zhu, M., et al., *Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective.* Contemp Clin Trials, 2020. **94**:105856.

230. Directorate of Health. *Covid-19 - antall innlagte pasienter på sykehus (rapporting avsluttet) [The number of inpatients with COVID-19 (reporting ended)],* 2020. [Online] Available from: https://www.helsedirektoratet.no/statistikk/antall-innlagte-pasienter-pa-sykehus-med-pavist-covid-19 [Accessed April 6 2022].

231. Norwegian Institute of Public Health. *Ukerapporter om koronavirus og covid-19 [Weekly update on the corona virus and COVID-19]*, 2022. [Online] Available from: https://www.fhi.no/publ/2020/koronavirus-ukerapporter/ [Accessed June 28 2022].

232. Norsk intensiv- og pandemiregister. *Norsk intensiv- og pandemiregister [Norwegian Intensive Care and Pandemic Registry]*, 2022. [Online] Available from: https://www.kvalitetsregistre.no/register/skade-og-intensiv/norsk-intensiv-og-pandemiregister [Accessed June 28 2022].

233. NOU 21:6, *Myndighetenes håndtering av koronapandemien - Rapport fra koronakommisjonen [The authorities´ handling of the COVID-19 pandemic - Report from the corona commission]*. 2021: Oslo.

234. Directorate of Health. *Befolkningsundersøkelse - covid-19 [Population based survey on COVID-19]*, 2021. [Online] Available from: https://www.helsedirektoratet.no/tema/beredskap-og-krisehandtering/koronavirus/befolkningsundersokelse-covid-19 [Accessed April 6 2022].

235. Kalager, M. and M. Bretthauger, *Innlegg: Flere av smitteverntiltakene ble innført uten grundige nok vurderinger i forkant*, in *Dagens Næringsliv*. 2021, dn.no: Oslo.

236. Norwegian Institute of Public Health. *Systematic evaluation of infection control measures*, 2021. [Online] Available from: https://www.fhi.no/en/more/norwegian-science-programme-on-covid19/Systematic-evaluation-of-infection-control-measures/ [Accessed April 4 2022].

237. Lai, C.K., *The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders.* Clin Interv Aging, 2014. **8**(9): p. 1051-1061.

238. Howard, R., et al., *Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease.* N Engl J Med, 2012. **366**(10): p. 893-903.

239. Kontopantelis, E., et al., *Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis.* BMJ, 2015. **350**:h2750.

240. Toot, S., et al., *Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis.* Int Psychogeriatr, 2017. **29**(2): p. 195-208.

241. Breitve, M.H., et al., *Apathy is associated with faster global cognitive decline and early nursing home admission in dementia with Lewy bodies.* Alzheimers Res Ther, 2018. **10**:83.

242. Wergeland, J.N., et al., *Predictors for Nursing Home Admission and Death among Community-Dwelling People 70 Years and Older Who Receive Domiciliary Care.* Dement Geriatr Cogn Dis Extra, 2015. **5**(3): p. 320-329.

243. Helvik, A.-S., et al., *The course of neuropsychiatric symptoms in nursing home residents from admission to 30-month follow-up.* PLoS One, 2018. **13**(10):e0206147.

244. Fog, A.F., et al., *Drug use differs by care level. A cross-sectional comparison between older people living at home or in a nursing home in Oslo, Norway.* BMC Geriatr, 2019. **19**:49.

245. Delgado, J., et al., *Continuity of GP care for patients with dementia: impact on prescribing and the health of patients.* Br J Gen Pract, 2022. **72**(715):e91-e98.

246. Welberry, H.J., et al., *Psychotropic medicine prescribing and polypharmacy for people with dementia entering residential aged care: the influence of changing general practitioners.* Med J Aust, 2021. **215**(3): p. 130-136.
247. Haugan, L., *Fastlegers oppfølging av sine hjemmeboende pasienter med demens [The regular general practitioners' follow-up of home-dwelling patients with dementia]*. 2020, The Norwegian Directorate of Health,: Oslo.
248. Gulla, C., *A Fine Balance: Drug Use in Norwegian Nursing Homes*. PhD Thesis, Norway: University of Bergen, 2018, p. 66.
249. Romskaug, R., et al., *Effect of Clinical Geriatric Assessments and Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Home-Dwelling Older Patients Receiving Polypharmacy: A Cluster Randomized Clinical Trial.* JAMA Intern Med, 2020. **180**(2): p. 181-189.
250. Gladhaug, A.F., *Drug use and drug-related problems in nursing homes: prevalence, changes following medication review and variation between institutions - Drug use and medication review in nursing homes in Oslo*. PhD Thesis, Norway: University of Oslo, 2021, p. 23.
251. Fog, A.F., et al., *Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway.* Scand J Prim Health Care, 2017. **35**(4): p. 329-335.
252. Thyrian, J.R., et al., *Effectiveness and Safety of Dementia Care Management in Primary Care: A Randomized Clinical Trial.* JAMA Psychiatry, 2017. **74**(10): p. 996-1004.
253. Smeets, C., et al., *Can the PROPER intervention reduce psychotropic drug prescription in nursing home residents with dementia? Results of a cluster-randomized controlled trial.* Int Psychogeriatr, 2021. **33**(6): p. 577-586.
254. Paolini, S., et al., *Perception of stress and cognitive efficiency in older adults with mild and moderate dementia during the COVID-19-related lockdown.* J Psychosom Res, 2021. **149**:110584.

255. Hanna, K., et al., *Emotional and Mental Wellbeing Following COVID-19 Public Health Measures on People Living With Dementia and Carers.* J Geriatr Psychiatry Neurol, 2022. **35**(3): p. 344-352.

256. Melby, L., et al., *Sykepleieres erfaringer med første fase av koronapandemien fra mars-oktober 2020 [Nurses' perspectives on the first wave of the Covid-19 pandemic Mar-Oct 2020], 2020.* SINTEF Digital Avd. Helse: Trondheim.

257. Tveito, M., M. Barca, and C.B. Hartberg, *Alderspsykiatriske helsetjenester under covid-19-pandemien [Psychogeriatric health care services during covid-19].* Tidsskr Nor Legeforen, 2021(9).

258. Eide, T.B., J. Straand, and A.M. Braend, *Good communication was valued as more important than accessibility according to 707 Nordic primary care patients: a report from the QUALICOPC study.* Scand J Prim Health Care, 2021. **39**(3): p. 296-304.

259. Øyane, N.M., et al., *Improving drug prescription in general practice using a novel quality improvement model.* Scand J Prim Health Care, 2021. **39**(2): p. 174-183.

260. Statistics Norway, *09933: Hours per week for home nursing and users of home help, by age, need for assistance, contents and year*. 2022, Statistics Norway: Oslo.

261. The Ministry of Health and Care Services, *Lov om pasient- og brukerrettigheter [Patient's Rights Act]* 1999: Oslo.

9. Appendix

9.1 Residency and care regime characteristics in Norway

Table 9.1 Residency and care regime characteristics in Norway

Residency	**Residential care regime [16, 18]**	**Care service characteristics**	**Medical services**[1]
Ordinary housing (‘egen bolig’)	Independent housing	Ambulatory homecare[2] and respite care[3] according to indication.	GP[4]
Assisted housing (‘omsorgsbolig’)	Independent housing	Ambulatory homecare[2] in staffed or unstaffed facilities and respite care[3] according to indication.	GP[4]
Nursing home (‘sykehjem’)	Institutional care	Patients[5] receiving integrated health care.	Nursing home physician[6]

Table legends: [1]Ambulatory on-call physicians provide primary care out-of-hours services, while secondary health care services (i.e., outpatient or inpatient) are referred to as needed. [2]Ambulatory homecare, on average 13-22 hours of home nursing and home care per week for older adults with an extensive need for assistance during 2019-2022 [260]. [3]Day care and respite care at a nursing home occasionally or at fixed intervals [18, 36]. [4]The regular general practitioner (GP) scheme entitles everyone who is registered as a resident in a Norwegian municipality with a GP. In the event of nursing home admittance, the PwD remains registered with his/her GP, even though responsibility for the PwD is transferred to the nursing home [125]. [5]Patient: a person who contacts the health care service requesting health care, or whom the health care service provides with or offers health care [261]. [6]Most physicians in nursing homes are GPs with visiting hours [129, 250].

9.2 Search strategy

The studies referred to in Table 1.5 were identified in the following search (conducted up until July 1, 2022), confined to original research in BPSD published in English or a Scandinavian language, excluding case reports, and extended on by snowballing: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=titles&SEARCHNAME=MESH_Psykotropics_BPSD&SEARCHTYPE=sdi&SEARCHLEVEL=pin&D=ppez

The studies referred to in Table 1.6 were identified in the following search (conducted up until September 1, 2022), confined to longitudinal non-intervention research published in English or a Scandinavian language, excluding case reports: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=titles&SEARCHNAME=ElderlyPandemicPsychiatricSymptoms&SEARCHTYPE=sdi&SEARCHLEVEL=pin&D=ppez.

A librarian at UiB consulted on both the aforementioned search strategies.

The general literature search for this thesis was completed September 9, 2022.

9.3 The COSMOS trial

9.3.1 Ethical approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Arne Salbu	55978498	27.02.2014	2013/1765/REK vest
			Deres dato:	Deres referanse:
			24.01.2014	

Vår referanse må oppgis ved alle henvendelser

Bettina Husebø
UiB

2013/1765 Forbedret mental helse hos pasienter boende på sykehjem. En klynge randomisert studie. (KOSMOS studien)

Forskningsansvarlig: Universitetet i Bergen
Prosjektleder: Bettina Husebø

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 13.02.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
KOSMOS er et akronym for KOmmunikasjon, Smertevurdering og behandling, Medikamentgjennomgang,Occupational Therapy og Sikkerhet og innebærer at man «kombinerer mest effektive forskningsresultater for å øke personalets kompetanse, pasientens velvære, sikkerhet, og livskvalitet. Deltakerne i studien er 310 pasienter fra 38 sykehjem (langtids- eller demensavdelinger), pluss «alle pårørende i informasjonssamtaler». Det opplyses generelt at 80 % av sykehjemsbeboerne er demente og de forventer at 60 % har moderat til alvorlig demens. Deltagerne vil inkluderes fra de samme sykehjem som i prosjekt 2013/1474 som ble behandlet av REK 19 september 2013. Deltakelse innebærer testing med spørreskjema for vurdering av livskvalitet, mental helse, mulig demnes og smerte. Noen kan også være aktuelle for en delstudie for måling av søvn og søvnrytme og disse vil bære aktigraf. Studien er organisert med intervensjonsgruppe og kontrollgruppe, hvor deltakelse i intervensjonsgruppen innebærer «en systematisk innsats for å øke sykehjemsavdelingens kompetanse og fokus på kommunikasjon, smertevurdering/smertebehandling, aktivitetstilbud og medikamentliste gjennomgang». Det presiseres at man ikke prøver ut ny behandling, men at en prøver å sette sammen enkeltbehandlinger som tidligere har vist seg å ha en positiv effek Komiteen hadde en rekke, spørsmål og merknader til opprinnelig søknad. Det foreligger svar på komiteens tilbakemelding.

Vurdering

Prosjektet er en stor implementeringsstudie som inneholder en rekke ulike elementer som har trekk av både opplæring, evaluering og forskning. Samlet sett fremstår prosjektet som vitenskapelig viktig og samfunnsnyttig, ikke minst sett ut fra de utfordringer norsk helsevesen står overfor, og vi tror prosjektet vil generere mye ny og viktig kunnskap.

Det er redegjort for oppbevaring av data. Vi ber om at dette ordnes i samråd med det stedlige personvernombud og at en benytter UiBs forskningsserver.

Godkjenningen gjelder frem til 31.12.17.

Besøksadresse:
Armauer Hansens Hus (AHH), Tverrfløy Nord, 2 etasje. Rom 281. Haukelandsveien 28...

Telefon: 55975000
E-post: rek-vest@uib.no
Web: http://helseforskning.etikkom.no/

REK Vest har ikke flere merknader.

Vedtak
REK vest godkjenner prosjektet i samsvar med forelagt søknad.

Sluttmelding og søknad om prosjektendring

Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.06.2018, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Ansgar Berg
Prof. Dr.med
Komiteleder

Arne Salbu
rådgiver

Kopi til: postmottak@uib.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Fredrik Rongved	55978498	11.02.2019	2013/1765/REK vest
			Deres dato:	Deres referanse:
			07.01.2019	

Vår referanse må oppgis ved alle henvendelser

Bettina Husebø
Institutt for global helse og samfunnsmedisin

2013/1765 Forbedret mental helse hos pasienter boende på sykehjem. En klynge randomisert studie. (KOSMOS studien)

Forskningsansvarlig: Universitetet i Bergen
Prosjektleder: Bettina Husebø

Vi viser til søknad om prosjektendring datert 07.01.2019 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK vest på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering

Ønsket endring:

Prosjektleder ønsker å endre prosjektslutt fra 31.12.2017 til 31.12.2024 samt ti nye prosjektmedarbeidere.

Prosjekttiden er overskredet med ett år. Prosjektleder skriver at det har foregått en alvorlig misforståelse da prosjektet ble søkt godkjent i 2013. Ved spørsmål om varighet oppga prosjektleder tidsperioden hvor prosjektet hadde finansiering fra Norges forskningsråd, og feilen ble ikke oppdaget før nå.

Pasientinklusjon og datainnsamling ble avsluttet i løpet av 2017. Det foreligger imidlertid nye data i prosjektet som enda ikke er analysert, og prosjektleder planlegger nye analyser på materialet.

Til slutt oppgir prosjektleder seks grunner til at prosjektendringen er forsvarlig:

1. Den opprinnelige sluttdatoen var satt ved en misforståelse, det tar tid å analysere store datasett.
2. Pasientinklusjon og datainnsamling ble ferdigstilt innen 2017. Det er ikke og skal ikke bli inkludert nye pasienter eller prosedyrer etter denne datoen.
3. Myndighetene oppfordrer til bruk av eksisterende data, istedenfor å gjennomføre nye studier som kan være tidkrevende for eldre med sammensatte sykdommer.
4. Fordelen er at mange stipendiater i inn- og utlandet i fremtiden kan ha bruk for disse data.
5. Stipendiater som nå skal begynne med prosjektet LIVE@Home.Path kan begynne å skrive sin første artikkel i avhandlingen basert på KOSMOS-data.
6. Kommer ikke på noen ulemper med en forlengelse av prosjektet.

REK vest ved leder behandlet saken.

Vurdering:

REK vest har ingen innvendinger mot at det legges til nye prosjektmedarbeidere.

REK vest er enig i at det er alvorlig å overskride prosjektslutten med ett år. REK er også enig i materialets nytteverdi og finner at prosjektleder har gitt gode argumenter for en forlengelse av prosjektet. REK vest godkjenner dermed prosjektforlengelse.

I endringsmeldingen er det også opplyst at prosjektgruppen forventer at prosjektet vil "leve lenge". REK vest vil her gjøre oppmerksom på at den beste måten for å tilrettelegge for lengre oppbevaring av data, og mulig videre forskning, er å opprette et helseregister for forskning. Et register vil gi prosjektgruppen tillatelse for lengre oppbevaring av data enn et prosjekt. Forskningsprosjekter er tidsbegrenset, og dermed vil det til slutt bli vanskelig med ytterligere forlengelse av prosjektet og da også datasettet. Etter den nye personvernforordningen er det lokalt personvernombud som kan opprette slike registre, i dette tilfellet personvernombudet ved Universitetet i Bergen. Avhengig av personvernombudets vurdering kan opprettelse av et slikt register innebære behov for å innhente nytt samtykke fra de registrerte.

Til sist forutsetter REK vest at stipendiatene i prosjektet *"LIVE@Home.Path"* vil behandle data fra KOSMOS-prosjektet i tråd med protokollen som er godkjent i KOSMOS-prosjektet.

REK vest har i dette vedtaket bare vurdert prosjektforlengelse og nye prosjektmedarbeidere.

Vedtak

REK vest godkjenner prosjektforlengelse og nye prosjektmedarbeidere i samsvar med forelagt søknad, med hjemmel i helseforskningsloven § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningsloven § 10 og forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
Prof. dr.med.
Komiteleder

Fredrik Rongved
rådgiver

Kopi til: *post@uib.no*

9.3.2 Consent forms

UNIVERSITETET I BERGEN

Institutt for global helse og samfunnsmedisin

KOSMOS

Forespørsel om deltakelse i forskningsprosjektet

«KOSMOS»

(**K**ommunikasjon, **S**mertevurdering/smertebehandling, **O**ccupational therapy (aktivitet) og **M**edikamentliste gjennomgang)

Kjære ……,

Vi kontakter deg, fordi vi ønsker å gjennomføre en undersøkelse om effekten av et økt fokus på 4 viktige aspekter på sykehjem: kommunikasjon, smertevurdering/smertebehandling, aktivitetstilbud og medikamentliste gjennomgang. KOSMOS prosjektet ønsker å fange hele mennesket for å øke livskvalitet. Programmet inkluderer et opplæringsprogram for personalet, oppfølging og implementering i pasientens hverdag.

Nedenfor gis en oversikt over hva undersøkelsen innebærer. Ta den tiden du trenger til å avgjøre om du ønsker å delta i undersøkelsen. Diskuter gjerne vår forespørsel med familien din.

Hva innebærer studien?

I studien vil vi teste deg med anerkjente spørreskjema for å vurdere graden av livskvalitet, demens, og smerte. Det er mulig at du trekkes ut til å delta i en delstudie der du vil ha på en «aktigraf», et ur som måler søvn og aktivitetsrytme. Du vil få en grundig undersøkelse av din ansvarlige sykehjemslege og prosjektleder.

I løpet av studien skal avdelinger ved deltakende sykehjem fordeles i "behandlingsgrupper" og "kontrollgrupper". Pasienter i behandlingsgruppen vil oppleve en systematisk innsats for å øke sykehjemsavdelingens kompetanse og fokus på kommunikasjon, smertevurdering/smertebehandling, aktivitetstilbud og medikamentliste gjennomgang. Dette innebærer omfattende kursing hos pleiepersonalet, og økt dokumentasjon av behandlingen og pleien du mottar. De sykehjemmene som blir «kontrollsykehjem» vil bli tilbudt kursing og oppfølging etter studiet er over.

Mulige fordeler

Vår forskergruppe antar at en slik kompetansehevning innebærer fordel for deg, som fører til økt livskvalitet, og reduksjon av problemer knyttet til mental helse. Velkjente pleie- og behandlingstiltak blir nå systematisk satt sammen, med en skreddersydd behandling rettet mot deg. Det understrekes, at studien ikke prøver ut ny behandling, men forsøker å sette sammen enkeltbehandlinger som tidligere er vist å ha en positiv effekt for sykehjemspasienter. Studien vil foregå i 9 måneder med vurderinger ved oppstart og etter 4 og 9 måneder. Måling av aktivitets- og søvnrytme finner sted ved oppstart og etter 4 måneder.

Gateadresse:	Postadresse:	Telefon:	Internett
Kalfarveien 31	5020 BERGEN	55 58 60 53	www.uib.no/sefas

UNIVERSITETET I BERGEN
Institutt for global helse og samfunnsmedisin

KOSMOS

Hva skjer med pasient informasjonen?
Informasjonen som registreres skal kun brukes i hensikten med studien. Alle opplysninger behandles uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Informasjonen skal slettes når prosjektet er gjennomført i 2015.

Frivillig deltakelse
Det er helt frivillig å delta i studien. Du kan når som helst, uten å oppgi noen grunn, trekke tilbake samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling.

Dersom du onsker å delta, undertegner du samtykkeerklæringen på siste side.

Ansvarlige
Studien vil bli gjennomført av undertegnede og Elisabeth Flo, psykolog og PhD, ved Institutt for global helse og samfunnsmedisin, Universitetet i Bergen.
Når du signerer vedlagte informasjonsskjema, bekrefter du at du har mottatt dette informasjonsbrevet denne undersøkelsen og en eventuell individuell smertebehandling.
Dersom du har spørsmål eller kommentarer, er du velkommen til å ta kontakt med Irene Aasmul (stipendiat): 411 64 544 eller Christine Gulla (stipendiat): 997 27 104.

Vennlig hilsen

Bettina Husebo, PhD
Institutt for global helse og samfunnsmedisin, Universitetet i Bergen
Kalfarveien 31
5020 Bergen

UNIVERSITETET I BERGEN
Institutt for global helse og samfunnsmedisin

KOSMOS

Samtykke til deltakelse i studien

INFORMASJONSSKJEMA

Jeg gir med dette mitt samtykke til å delta i studien for å undersøke smerte og atferdsforandringer i forbindelse med demens. Denne studien innholder også en individuell medikamentell smertebehandling av mulige smerteplager.

Jeg er klar over at forskerteamet ønsker å registrere opplysninger om sykdommer og oppholdstid på sykehjem fra journalen min. Opplysninger behandles konfidensielle og kun informasjoner som er nødvendige for studien vil bli innhentet.

Jeg er klar over at samtykket er frivillig og at jeg når som helst kan trekke samtykket tilbake uten ytterligere grunngiving, og at dette ikke vil få innvirkning på min fremtidige oppfølging eller behandling ved sykehjemmet.

....
Signatur (pasient) Dato

.....
Navn i blokkbokstaver

Gateadresse: Kalfarveien 31 | Postadresse: 5020 BERGEN | Telefon: 55 58 60 53 | Internett www.uib.no/sefas

UNIVERSITETET I BERGEN
Institutt for global helse og samfunnsmedisin

Samtykke til deltakelse i studien

Det foreligger ingen holdepunkter for at pasienten _____
ikke ville ha deltatt i denne studien av effekten av et økt fokus på 4 viktige aspekter på sykehjem: kommunikasjon, smertevurdering/smertebehandling, aktivitetstilbud og medikament-gjennomgang.

Jeg er klar over at forskerteamet ønsker å registrere opplysninger om sykdommer og oppholdstid på sykehjem fra pasientens journal. Opplysninger behandles konfidensielt og kun informasjon som er nødvendig for studien vil bli innhentet.

Jeg er klar over at pasientens deltakelse er frivillig og at pasienten når som helst kan trekke seg tilbake uten ytterligere grunngiving, og at dette ikke vil få innvirkning på pasientens fremtidige oppfølging eller behandling ved sykehjemmet.

_____ _____

Signatur (pårørende) Dato

Gateadresse: Kalfarveien 31 | Postadresse: 5020 BERGEN | Telefon: 55 58 60 53 | Internett: www.uib.no/sefas

9.3.3 Report utilized in the medication reviews

Pasientnavn	Alder	BMI	BT	Puls	MOBID-2	CSDD	NPI depresjon	MMSE	FAST	CMAI	NPI	Qualid	ADL	Interaksjon grønn	Interaksjon gul	Interaksjon rød

Gjennomsnittlig antall faste legemidler:

Gjennomsnittlig antall legemidler ved behov:

Gjennomsnittlig antall legemidler totalt:

Interaksjoner:

9.3.4 Sensitivity analysis, Paper I

Table 9.2 Changes within the intervention and control group at four months vs. baseline for patients with a diagnosis of dementia in their medical record (n=274) amongst the 428 included in Paper I from COSMOS

	Intervention (n = 141)			**Control** (n = 133)			P-value*
	mean	(SD)	n	mean	(SD)	n	
Drugs in general							
Total number	-1.51	(2.59)	141	-0.37	(1.85)	133	<0.001*
Regularly	-1.08	(2.04)	141	-0.31	(1.59)	133	<0.001*
Psychotropic drugs							
Total number	-0.49	(1.02)	141	-0.05	(0.74)	133	<0.001*
Regularly	-0.29	(0.81)	141	-0.02	(0.62)	133	0.002*
≥1 regularly	-0.47	(0.87)	100	-0.08	(0.68)	98	0.006*
≥3 regularly	-1.14	(1.08)	22	-0.19	(0.68)	21	0.002*
Classes regularly prescribed							
Antipsychotic drugs	-0.01	(0.34)	141	0.02	(0.25)	133	0.542
Anxiolytic drugs	-0.03	(0.34)	141	0.00	(0.33)	133	0.479
Hypnotic/sedative drugs	-0.09	(0.39)	141	0.05	(0.33)	133	0.002*
Antidepressant drugs	-0.12	(0.50)	141	-0.05	(0.40)	133	0.212**
Antidementia drugs	-0.05	(0.32)	141	-0.04	(0.23)	133	0.720
Behavioral and psychological symptoms of dementia							
NPI-NH							
Total score	-2.21	(21.40)	140	-2.15	(19.91)	128	0.982
Domains							
Delusions	-0.20	(3.61)	139	-0.40	(3.51)	129	0.644
Hallucinations	0.01	(2.24)	141	-0.06	(2.45)	130	0.811
Agitation	-0.72	(3.62)	137	-0.72	(3.67)	130	0.999
Depression	-0.37	(4.04)	138	-0.31	(2.94)	127	0.885
Anxiety	0.05	(3.87)	138	-0.52	(4.00)	129	0.238
Euphoria	-0.07	(1.54)	138	0.20	(2.28)	129	0.267
Apathy	-0.23	(3.33)	140	0.33	(2.87)	125	0.145
Disinhibitions	0.10	(2.92)	140	0.00	(3.41)	128	0.798
Irritability	-0.71	(4.00)	136	-0.55	(3.78)	128	0.741

Aberrant motor behavior	-0.26	(3.07)	137	-0.21	(3.76)	129	0.899
Sleep disturbances	-0.09	(2.50)	140	-0.19	(2.91)	130	0.766
Appetite changes	0.27	(3.48)	139	0.35	(2.06)	128	0.806
CSDD							
Total score	-0.04	(5.91)	139	-0.25	(6.02)	130	0.781
Level of functioning							
Physical Self-Maintenance Scale total score	0.22	(4.44)	141	0.43	(3.77)	131	0.677**
Toileting	0.09	(1.39)	141	0.04	(1.34)	130	0.747
Feeding	0.21	(0.99)	141	0.10	(0.81)	130	0.304
Dressing	0.02	(1.13)	141	0.18	(0.98)	130	0.204
Grooming	-0.03	(1.02)	141	0.12	(0.86)	129	0.208
Physical ambulation	0.04	(0.88)	141	0.08	(0.72)	131	0.671
Showering	-0.12	(1.19)	141	-0.04	(1.25)	130	0.580

Table legends: NPI-NH: Neuropsychiatric Inventory Nursing Home Version. CSDD: Cornell Scale of Depression in Dementia. * P <0.05, **P <0.05 in Paper I, while >0.05 in the current analysis.

9.4 The LIVE@Home.Path trial

Table 9.3 The phases in developing LIVE@Home.Path

Phase (year)	Title	Sponsors	Approvals	Registrations
Pre-project	ICI-HomeTime	RCN 261626		
	Helhetlig behandlingsforløp demens, til nytte for pasientene, familienettverket og helsetjenestene	RCN 261605		
Feasibility study (2017-2019)	"What matters to me?"	The Dam Foundation (2016/FO77186), The Norwegian Women's Public Health Association as applicant organization	REC North Norway 2017/1519	ClinicalTrials.gov: NCT04043364 (retrospectively registered)
Cluster randomized controlled trial (2019-2021)	LIVE@Home.Path	RCN 273581, The Dignity Centre	REC North Norway 2019/385 NSD 514093	ClinicalTrials.gov: NCT04043364 DPIA ePhorte 2019/5569

Table legends: RCN: The Research Council of Norway Sponsor's Protocol Code; REC: Regional Committee for Medical and Health Research Ethics; NSD: Norwegian Centre for Research Data; DPIA: Data Protection Impact Assessment. ePhorte: University of Bergen Archive reference.

9.4.1 Ethical approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			29.03.2019	2019/385/REK nord
			Deres dato:	Deres referanse:
			12.02.2019	

Vår referanse må oppgis ved alle henvendelser

Bettina Husebø
Institutt for global helse og samfunnsmedisin

2019/385 LIVE@Home.Path: Hva er viktig for deg? En intervensjonsstudie for hjemmeboende med demens og deres pårørende

Forskningsansvarlig institusjon: Universitetet i Bergen
Prosjektleder: Bettina Husebø

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 14.03.2019. Vurderingen er gjort med hjemmel i helseforskningsloven § 10.

Prosjektleders prosjektomtale
Pasienter, pårørende og helsemyndigheter er pådrivere for at personer med demens skal bo hjemme så lenge og så godt som mulig. LIVE@Home.Path skal utvikle, teste og implementere en kompleks intervensjon med fokus på Learning, Innovation, Volunteers og Empowerment ved hjelp av kvantitative undersøkelser for å belyse om dette reduserer belastningen for familien og bedrer ressursutnyttelsen i helsetjenesten. Ved hjelp av en randomiseringsprosess i flere trinn over tid (randomised stepped-wedge controlled trial) vil vi tilby alle de ca 315 inkluderte pasientene og deres pårørende intervensjonen og vil sammenligne resultater mellom gruppene på ulike tidspunkt for å undersøke om intervensjonen har effekt på 1) Ressursbruk for pårørende, inkl tidsbruk og hvor lenge pas kan bo lengre hjemme 2) belastning for pasient, målt ved psykiatriske symptomer, livskvalitet og kvalitative intervju om frivillighet 3) belastning for pårørende målt ved belastningskalaer.

Om prosjektet
Hovedformålet med studien er å undersøke om intervensjonen LIVE (Learning, Innovation, Volunteers and Empowerment) har effekt på tid brukt av pårørende og pårørendes opplevelse av belastning knyttet til personen med demens.

Prosjektet er en multisenterstudie som skal gjennomføres i Bergen, Bærum og Kristiansand kommune. Universitet i Bergen er forskningsansvarlig.

Prosjektet er en del av en ph.d.-utdanning i medisin.

Deltakere/rekruttering/samtykke
Det skal rekrutteres totalt 315 personer til studien i Bergen, Bærum og Kristiansand kommune; 35 x 3 personer med demens og deres pårørende.

Deltagere vil bli rekruttert fra hjemmetjenesten, fastleger og hukommelsesklinikker i spesialisthelsetjenesten. I tillegg skal det inngå koordinatorer, ansatte i hjemmetjenesten, som skal

gjennomføre deler av intervensjonen. Det skal knyttes en koordinator til hver pasient/pårørende.

Det er ikke redegjort for hvordan rekrutteringen rent faktisk skal skje. Dersom forskningsdeltakeren kan anses å være i et avhengighetsforhold til den som ber om samtykke slik at forskningsdeltakeren vil kunne føle seg presset til å gi samtykke, skal det informerte samtykket innhentes av en annen som forskningsdeltakeren ikke har slikt forhold til, jf. helseforskningsloven § 13.

Et eventuelt samtykke til deltakelse må kunne leveres/sendes inn på eget initiativ til prosjektet. REK forutsetter at disse prinsippene vil bli ivaretatt i prosjektet.

Prosjektet vil inkludere personer med redusert samtykkekompetanse og i prosjektsøknaden presiseres at pårørende, i tillegg til pasient, må samtykke til deltagelse. Det følger videre av søknaden at: *«Vi er spesielt oppmerksom på å tilby tilpasset informasjon om studien og hva deltagelse innebærer til pas og pårørende. Studier har vist at generell samtykkekompetanse er bevart inntil MMS lik 17, noe som utgjør majoriteten av de vi ønsker å inkludere til studien. Uavhengig av stadium av kognitiv svik vil pårørende også bli inkludert, og vil således være i stand til å ivareta deltager sine interesser slik de kjenner vedkommende også fra før start av demenssykdommen.»*

Data
Det skal innhentes data om pasientenes diagnoser og medikamentbruk fra pasientjournal hos fastlege og hjemmetjeneste.

Det skal innhentes data om ressursbruk og pårørendes belastning, livskvalitet, nevropsykiatriske symptomer, kognitive funksjoner, smerte, funksjonsnivå (ADL), samt demografiske data gjennom utfylling av spørreskjema for pasienten og pårørende.

Når det gjelder håndtering av data etter prosjektslutt følger det av søknaden at: *«Vi følger fremdeles de nødvendige sikkerhetstiltak, og vil søke om å videre bruke data for best mulig utnyttelse av verdifulle data om en sårbar pasientgruppe.»* REK presiserer at hovedregelen etter helseforskningsloven er at data kan oppbevares i inntil 5 år etter prosjektslutt, men da kun for kontrollhensyn. Data skal da anonymiseres (sletting av koblingsnøkkel) eller slettes. Dersom data skal oppbevares lengre enn dette eller for andre formål enn i dette spesifikke prosjektet, må prosjektleder redegjøre nærmere for dette, herunder hvordan data tenkes benyttet og til hvilke formål. Det må eventuelt også tas høyde for gjenbruk i samtykkeskrivene.

Prosjektstart er i søknaden satt til 1.1.2019. REK forutsetter at datainnsamling ikke påbegynnes før endelig godkjenning foreligger.

Samarbeid med utlandet
Det er opplyst i prosjektsøknaden at prosjektet har samarbeid med Storbritannia, Japan, Hongkong, USA og Nederland.

Informasjons-/samtykkeskriv
I alle 3 oversendte informasjons-/samtykkeskriv må tittel på prosjektet være lik den faktiske tittelen på prosjektet, herunder: *«LIVE@Home.Path: Hva er viktig for deg? En intervensjonsstudie for hjemmeboende med demens og deres pårørende»*

I alle de 3 skrivene må innledningen omskrives slik at det fremkommer at dette er en forespørsel om deltakelse i forskningsprosjektet.

I alle de 3 skrivene må det inntas at dataene vil slettes senest 5 år etter prosjektslutt og ikke etter 10 år, jf. overfor under *«Data»*. Eventuelt må deltakerne samtykke eksplisitt til en utvidet bruk av dataene eller at de samtykker til at koblingsnøkkel ikke slettes og at de kan kontaktes på et senere tidspunkt for nytt samtykke til eventuell bruk av data i andre prosjekter.

I alle de 3 skrivene må det inntas informasjon om personvern og oppbevaring av personopplysninger i tråd med ny personopplysningslov. Det anbefales at revidert mal for samtykkeskriv på REKs hjemmesider

benyttes.

I alle de 3 skrivene må det inntas at noen av deltakerne også vil bli forespurt om å gjennomføre intervjuer, jf. protokollen s. 58.

Ettersom prosjektet har samarbeid med utlandet og skal overføre data til utlandet må dette inntas i alle 3 informasjons-/samtykkeskrivene. REK anbefaler at revidert mal for samtykkeskriv på REKs hjemmesider benyttes til utforming av dette punktet.

I informasjons-/samtykkeskrivet til personen med demens må det inntas at det også samtykkes til at prosjektet kan innhente data gjennom pårørende og helsepersonell som har kontakt med pasienten.

I informasjons-/samtykkeskrivet til de pårørende må det inntas at det også samtykkes til at prosjektet kan innhente data fra helsepersonell som har kontakt med den pårørende.

I informasjons-/samtykkeskrivet til personen med demens og til de pårørende synes tidsestimatet for datainnsamling (en-to timer) for lavt i forhold til de omfattende skjema som faktisk skal fylles ut og de eventuelle intervjuer som skal gjennomføres. Dette må oppjusteres til et mer realistisk timeantall.

Dersom den pårørende skal samtykke på vegne av pasienten, og ikke kun på vegne av seg selv, må det utarbeides et eget informasjons-/samtykkeskriv for dette, eventuelt må dette inntas i skrivet for de pårørende og de må eksplisitt samtykke både på vegne av seg selv og på vegne av pasienten.

Vedtak
REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider og godkjenner det med hjemmel i helseforskningsloven § 10.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Før prosjektet kan igangsettes må det sendes inn reviderte informasjonsskriv. Skrivene sendes som vedlegg i e-post til post@helseforskning.etikkom.no.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.6.2031, jf. helseforskningsloven § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Kopi til: Bettina.Husebo@uib.no;
post@uib.no

9.4.2 Consent forms

Samtykkeskjema til personen med demens, LIVE@Home.Path

LIVE@HOME.PATH: HVA ER VIKTIG FOR DEG?

En intervensjonsstudie for hjemmeboende med demens og deres pårørende

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke hvordan personer med demens kan bo trygt og godt hjemme så lenge som mulig. I studien vil vi undersøke effekten av opplæring og kurs til dine omsorgspersoner, nytten av en fast koordinator, bruk av velferdsteknologi, engasjement av frivillige og myndiggjøring i beslutningsprosesser. Sentralt er spørsmålet: «Hva er viktig for deg?». Studien gjennomføres av Senter for Alders og Sykehjemsmedisin ved Universitetet i Bergen.

Hva innebærer deltagelse for deg?

Studien varer i to år. I deler av denne perioden får du tett oppfølging av en fast koordinator, og i etterkant regelmessige telefonsamtaler og hjelp etter behov. Koordinator kan hjelpe deg å komme i kontakt med frivillige tjenester, informere om aktuelle kurstilbud og være bindeleddet til andre helsetjenester. Målet er at koordinator er den ene personen dere kontakter når dere har behov for kommunal helsehjelp. Vi vil kontakte deg hvert halvår for å fylle ut ulike skjema, der vi kartlegger din bakgrunn, helsetilstand, livskvalitet og daglige funksjon. Tidspunkt avtales med deg i forkant. Informasjonen som kommer frem ved kartleggingen vil koordinator bruke for å gi deg god oppfølging basert på dine behov. Fastlegen din vil kontaktes for opplysninger om din medisinbruk og dine diagnoser. Pårørende og helsepersonell som du har kontakt med kan også bidra med opplysninger, som for eksempel medikamentbruk. Vi anbefaler også regelmessig gjennomgang av medisinene du bruker hos fastlegen din. Deltagelse kan også innebære at lege(r) fra forskningsgruppen deltar i medikamentvurderinger hos fastlegen din. Enkelte deltagere vil også kontaktes for intervjuer.

Mulige fordeler og ulemper

Vi tror at en fast koordinator i kommunale helsetjenester gjør hverdagen lettere og bedre for personer med demens. Vi tror også at hverdagen for din pårørende lettes. Kontakt med koordinator justeres etter dine behov. Vi tror at koordinator gjør at tiden dere er i kontakt med kommunehelsetjenesten blir mer konstruktiv, siden denne personen kjenner din situasjon. Mulig ulempe ved deltagelse er at du må sette av tid til kartlegging, som avklares på forhånd. Vi tror kartleggingen tar mellom en og tre timer hvert halvår.

Frivillig deltakelse og mulighet for å trekke sitt samtykke

Det er frivillig å delta i forskningsprosjektet, og dersom du ikke ønsker å delta påvirker det ikke dine rettigheter i helsetjenesten. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på neste side. Diskuter gjerne deltagelse med andre familiemedlemmer. Du kan når som helst trekke ditt samtykke uten begrunnelse. Dette vil ikke få konsekvenser for dine rettigheter knyttet til helsehjelp. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte din lokale prosjektkontakt_____ eller prosjektleder professor Bettina Husebø.

Samtykkeskjema til personen med demens, LIVE@Home.Path

Hva skjer med opplysningene om deg?

Vi skal ikke bruke informasjonen om deg til annet enn denne studien (se beskrivelse i informasjonsbrev). Du har rett til innsyn i registrert informasjonen og tiltak for sikring av disse. Du har rett til å korrigere eventuelle feil. En kode knytter ditt navn til registrert informasjon, og denne er lagret adskilt og under beskyttelse. Alle opplysningene behandles anonymt av tilknyttede forskere. Data skal anonymiseres senest 5 år etter prosjektslutt.

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (REK Nord 2019/385). All informasjon oppbevares i henhold til ny personopplysningslov. Etter ny personopplysningslov har behandlingsansvarlig, Universitetet i Bergen, og prosjektleder Bettina Husebø ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet. Lagringen vi bruker er sikker og informasjonen kan ikke spores tilbake til deg.

Noen deltagere vil bli spurt om å gjøre intervjuer i tillegg. Vi ønsker også å kunne kontakte deg etter prosjektperioden på 2 år dersom vi vil gjøre en oppfølgingsstudie.

Vi samarbeider med forskere i EU/EØS, og avidentifisert informasjon om deg vil kunne overføres til disse i utlandet. Samarbeidspartnere fra Japan og USA kan få tilgang til data dersom de oppholder seg i Norge. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte og i henhold til EUs personvernforordning. Koden som knytter deg til dine personidentifiserbare opplysninger vil ikke bli utlevert. Resultatene vil bli publisert i internasjonale tidsskrift, på internasjonale og nasjonale konferanser og i generelle nyhetsmedier, slik at kunnskapen du har bidratt med i studien kommer flest mulig til gode.

Kontaktopplysninger

Dersom du har spørsmål til prosjektet kan du kontakte din lokale prosjektkontakt _____. Eventuelt kan prosjektleder ved Senter for Alders og Sykehjemsmedisin ved Universitetet i Bergen, Bettina Husebø kontaktes: Bettina.husebo@uib.no, telefon: 55 58 67 35.

Jeg samtykker til å delta i prosjektet og til at opplysninger om meg brukes som beskrevet.

Sted og dato	Signatur, deltager
	Navn med blokkbokstaver, deltager
	Navn i blokkbokstaver, den som har informert

LIVE@HOME.PATH: HVA ER VIKTIG FOR DEG?

En intervensjonsstudie for hjemmeboende eldre med demens og deres pårørende

Dette er et spørsmål til deg om deltagelse i et forskningsprosjekt for å undersøke hvordan personer med demens kan bo trygt og godt hjemme så lenge som mulig, med fokus også på den pårørende. Vi ønsker å teste om en fast koordinator/kontaktperson i hjemmesykepleien kan bidra til avlasting og bedre livskvalitet for pårørende, bedre livskvalitet hos personer med demens, og samtidig være samfunnsøkonomisk bærekraftig. I studien vil vi undersøke effekten av opplæring og kurs, bruk av velferdsteknologi, kontakt med frivillige og myndiggjøring i beslutningsprosesser. Sentralt er spørsmålet: «Hva er viktig for deg?». Studien gjennomføres av Senter for Alders og Sykehjemsmedisin ved Universitetet i Bergen.

Hva innebærer deltagelse for deg?

Studien varer i to år. Du og din nære med demens vil følges tett av en koordinator i deler av denne perioden, og i etterkant med regelmessige telefonsamtaler og hjelp etter behov. Koordinator kan hjelpe dere å komme i kontakt med frivillige tjenester, informere om aktuelle kurstilbud og være bindeleddet til andre helsetjenester. Målet er at koordinator er den ene personen dere kontakter når dere har behov for kommunal helsehjelp knyttet til personen med demens som du har omsorg for. Vi vil kontakte dere hvert halvår for å fylle ut ulike skjema, som blant annet vil omhandle deres bakgrunn, helsetilstand, livskvalitet og daglige funksjon. Noen spørreskjema vil omhandle deg, andre vil omhandle personen med demens som du har omsorg for. Tidspunkt avtales med deg i forkant. Helsepersonell som er i kontakt med deg i forbindelse med personen med demens vil også kunne bidra med informasjon, for eksempel medikamentbruk. Dette gjør vi for å øke vår kunnskap, samt å følge deg opp som pårørende. Enkelte deltagere vil også kontaktes for intervjuer.

Mulige fordeler og ulemper

Vi tror at hverdagsutfordringer kan reduseres i studien, og at du og den du er pårørende for dermed får bedre livskvalitet. Deres kontakt med koordinatoren vil tilpasses individuelt. Vi tror at en fast koordinator medfører at tiden dere er i kontakt med kommunehelsetjenesten blir mer konstruktiv, siden koordinator kjenner deres situasjon godt. Vi tror kartleggingen vil ta mellom en og tre time og gjentas hvert halvår i studieperioden. Mulig ulempe ved deltagelse er at du må sette av tid til kartlegging, som avklares på forhånd.

Frivillig deltakelse og mulighet for å trekke sitt samtykke

Det er frivillig å delta i forskningsprosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på neste side. Diskuter gjerne deltagelse med andre familiemedlemmer. Du kan når som helst trekke ditt samtykke uten begrunnelse. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte din lokale prosjektkontakt_____ eller prosjektleder professor Bettina Husebø.

Hva skjer med opplysningene om deg?

Vi skal ikke bruke informasjonen om deg til annet enn denne studien (se beskrivelse i informasjonsbrev). Du har rett til innsyn i registrert informasjonen og tiltak for sikring av disse. Du har rett til å korrigere eventuelle feil. En kode knytter ditt navn til registrert informasjon, og denne er lagret adskilt og under beskyttelse. Alle opplysningene behandles anonymt av tilknyttede forskere. Data skal anonymiseres senest 5 år etter prosjektslutt.

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (REK Nord 2019/385). All informasjon oppbevares i henhold til ny personopplysningslov Etter ny personopplysningslov har behandlingsansvarlig, Universitetet i Bergen, og prosjektleder Bettina Husebø ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet. Lagringen vi bruker er sikker og informasjonen kan ikke spores tilbake til deg.

Noen deltagere vil bli spurt om å gjøre intervjuer i tillegg. Vi ønsker også å kunne kontakte deg etter prosjektperioden på 2 år dersom vi vil gjøre en oppfølgingsstudie.

Vi samarbeider med forskere i EU/EØS, og avidentifisert informasjon om deg vil kunne overføres til disse i utlandet. Samarbeidspartnere fra Japan og USA kan få tilgang til data dersom de oppholder seg i Norge. Prosjektleder vil sikre at dine opplysninger blir ivaretatt på en trygg måte og i henhold til EUs personvernforordning. Koden som knytter deg til dine personidentifiserbare opplysninger vil ikke bli utlevert. Resultatene vil bli publisert i internasjonale tidsskrift, på internasjonale og nasjonale konferanser og i generelle nyhetsmedier, slik at kunnskapen du har bidratt med i studien kommer flest mulig til gode.

Kontaktopplysninger

Dersom du har spørsmål til prosjektet kan du kontakte din lokale prosjektkontakt _____. Eventuelt kan prosjektleder ved Senter for Alders og Sykehjemsmedisin ved Universitetet i Bergen, Bettina Husebø kontaktes: bettina.husebo@uib.no, telefon: 55 58 67 35.

Jeg samtykker til å delta i prosjektet og til at opplysninger om meg brukes som beskrevet

Sted og dato	Signatur
	Navn med blokkbokstaver
	Samtykke til å bli kontaktet to år etter prosjektperioden

9.4.3 Information to the GPs

The coordinators established contact with the PwD's regular GP to inform on participation by sending an (adopted) version of the following message in the electronic medical record:

Kjære fastlege, *Pasientens navn* deltar i en nasjonal RCT studie (LIVE@Home.Path) og mottar nå intervensjonen. Studien undersøker om multikomponente tiltak i primærhelsetjenesten organisert gjennom en koordinator (sykepleier med spesialfunksjon lokalisert i demensteamene) kan lette situasjonen for eldre med demens/hukommelsessvikt og deres pårørende. Koordinator er ansatt i kommunen og vil ha minimum månedlig oppfølging av deltager.

Vi ønsker at alle deltagere bestiller time for:

1. Medikamentgjennomgang: bør fokusere på antikolinerge bivirkninger, samt medikamentenes nytte/risiko-profil og interaksjoner (se gjerne Sjekkliste for legemiddelgjennomgang utarbeidet av Legemiddelverket; https://legemiddelverket.no/Documents/Bivirkninger%20og%20sikkerhet/R%C3%A5d%20til%20helsepersonell/Legemiddelgjennomgang/Sjekkliste%20for%20legemiddelgjennomgang.pdf).
2. Forhåndssamtaler (Advanced Care Planning): ACP er en gjentagende prosess for økt sykdomsforståelse, verdidiskusjon, ønsker for fremtidige mål, samt juridiske forhold (feks: fremtidsfullmakt og verge) når pasienten selv ikke er i stand til å ta egne avgjørelser; https://tidsskriftet.no/2017/03/sprakspalten/forhandssamtaler-advance-care-planning.

Du vil motta en kortfattet oversikt om smerter, adferd, pårørendebelastning, kognitive ressurser, samt puls, blodtrykk og BMI datert før intervensjonsstart. Dersom demensdiagnose ikke er etablert, oppfordrer vi til fullstendig utredning (vurder MMSE, klokketest, lab. og eventuelt bildediagnostikk; https://aldring-og-helse-media.s3.amazonaws.com/documents/Leger_4s_Mars2011.PDF).

Med vennlig hilsen *koordinators navn* (telefonnummer)

9.4.4 Report utilized in the medication reviews

The coordinators provided the GPs in LIVE@Home.Path with the following report presenting results from clinical assessments.

Pasient-id:

Fødselsdato:

Dato:

Belastningsskala for pårørende	**RSS**: Gir overblikk av belastningen på omsorgsgivere. Jo høyere skåre, jo høyere belastning for pårørende. Skåre på mer enn 23 ansees betydelig, men ingen klare grenser er etablert. Range [0, 60].	
Smerter	**MoBID-2**: Jo høyere skåre, jo mer smerter. Totalskåre [0,10]	
Agitasjon	**CMAI:** Jo høyere skåre, jo større symptomtrykk. Range [29, 203].	
Depressive symptomer	**CSDD:** Jo høyere skåre, jo alvorligere symptombelastning. Range [0,38]. Skåre ≥7 indikerer depresjon, mens en skåre ≥ 12 indikerer depresjon av moderat til alvorlig grad.	
Adferdsmessige og psykologiske symptomer ved demens	**NPI:** Jo høyere skåre, jo mer frekvent og/eller uttalte symptomer. **Totalt:** Range [0,144]	
Kognisjon	**MMSE:** Jo bedre skåre, jo bedre kognisjon. Range [0,30]. Patologisk skåre < 24p.	
Spørre-skjema til pårørende	**IQCODE**: Vurderer kognitive endringer siste 10 år. Snitttskåre >3.5 sannsynliggjør demens. Jo høyere gjennomsnittsskåre, jo større begrensninger.	
KMI	Kg/m2. Undervektig < 18.4, Normalvektig 18.5-24.9, Overvekt 25.0-29.9, Fedme: >30	
Puls	Slag/min	
Blod-trykk	Systolisk/diastolisk, mmHg	
Rapport	**Forklaring**	

9.5 The PAN.DEM study

9.5.1 Ethical approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Maren Melsbø	77620748	06.04.2020	10861
			Deres referanse:	

Bettina Husebø

10861 LIVE@Home.Path: Hva er viktig for deg? En intervensjonsstudie for hjemmeboende med demens og deres pårørende

Forskningsansvarlig: Universitetet i Bergen

Søker: Bettina Husebø

REKs vurdering

Vi viser til søknad om prosjektendring for ovennevnte forskningsprosjekt mottatt 03.04.2020 samt tilleggsinformasjon mottatt samme dato. Søknaden er behandlet av sekretariatet i REK nord på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

Prosjektleder opplyser i endringssøknaden at endringen gjelder revidert informasjonsskriv med reservasjonsrett til pårørende som deltar.

REK har ingen innvendinger til den omsøkte endringen. Oversendt informasjonsskriv er godkjent for bruk.

Etter fullmakt er det fattet følgende

Vedtak

Godkjent

Med hjemmel i helseforskningsloven § 11 godkjennes prosjektendringen.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Maren Johannessen Melsbø
rådgiver

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

9.5.2 Information to the participants

INFORMASJONSBREV: PAN.DEM

Telefonintervju med pårørende om Covid-19
som tillegg til

LIVE@Home.Path-studien

Dette er et informasjonsbrev til deg som er pårørende og deltar i studien LIVE@Home.Path. LIVE@Home.Path er en intervensjonsstudie som undersøker hvordan personer med demens/hukommelsessvikt kan bo trygt og godt hjemme så lenge som mulig, med fokus også på den pårørende. Sentralt er opplæring og kurs, bruk av velferdsteknologi, kontakt med frivillige og myndiggjøring i beslutningsprosesser. Studien gjennomføres av Senter for Alders og Sykehjemsmedisin ved Universitetet i Bergen.

Den pågående Covid-19 pandemien har medført ekstraordinære tiltak og endret hverdagsliv for mange. Vi ønsker å undersøke situasjonen for hjemmeboende eldre med demens/hukommelsessvikt og deres pårørende under pandemien. Tema som berøres er forståelse og bekymring over pandemi-situasjonen, adferds- og psykologiske symptomer (APSD), helsetjenestebruk, sosialt nettverk, eventuelle frivillige tjenester, samt situasjonen i sin helhet.

Telefonintervju av pårørende vil gjennomføres som supplement til de halvårlige hjemmebesøkene som inngår i LIVE@Home.Path. Vi anslår at et intervju tar om lag 5-15 minutter.

Du har rett til å motsette deg datainnsamling, da det er helt frivillig å svare på disse spørsmålene. Dersom du ønsker å reservere deg, informerer du datainnsamler direkte når han/hun ringer deg, sender epost til live@uib.no / marie.gedde@uib.no eller ringer Marie Gedde: [redacted]. Å reservere seg mot telefonintervjuet vil verken påvirke rett til helsehjelp eller deltagelse/ytterligere tjenester som del av LIVE@Home.Path-studien. Du kan når som helst trekke tilbake dine opplysninger, endre eventuelle feil, eller gi andre tilbakemeldinger ved å sene epost til live@uib.no eller kontakte Marie Gedde; [redacted]

Oppdateringen av forskningsprotokollen er i overensstemmelse med gjeldende lovverk og i sin helhet godkjent av Regional Etiske Komité (2019/385/REK Nord).

Med vennlig hilsen

Marie Gedde
PhD stipendiat,

På vegne av LIVE@Home.Path-gruppen ved Universitetet i Bergen, Høgskolen på Vestlandet, NORCE, Haraldsplass Diakonale Sykehus og Verdighetssenteret

Paper I

Gedde MH, Husebo BS, Mannseth J, Kjome RLS, Naik M, Berge LI: Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial. Am J Geriatr Psychiatry 2021;29(3):304-315.

Am J of Geriatric Psychiatry 29:3 (2021) 304–315

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Regular Research Article

Less Is More: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results From the Cluster-Randomized Controlled COSMOS Trial

Marie H. Gedde, M.D., Bettina S. Husebo, M.D., Ph.D., Janne Mannseth, M.Sc., Ph.D., Reidun L.S. Kjome, M.Sc., Ph.D., Mala Naik, M.D., Ph.D., Line I. Berge, M.D., Ph.D.

ARTICLE INFO

Article history:
Received June, 12 2020
Revised July, 8 2020
Accepted July, 8 2020

Key Words:
Deprescribing
medication review
psychotropic drugs
behavioral and psychological symptoms of dementia (BPSD)
neuropsychiatric symptoms (NPS)
activities of daily living (ADL)

ABSTRACT

Objective: *To investigate the impact of medication reviews using collegial mentoring and systematic clinical evaluation on psychotropic prescriptions, behavioral and psychological symptoms of dementia (BPSD), and activities of daily living (ADL).* ***Design:*** *Four-month multicenter, multicomponent, cluster-randomized, single-blinded controlled trial.* ***Setting:*** *Thirty-three Norwegian nursing homes including 67 nursing home wards (clusters).* ***Participants:*** *A total of 723 enrolled patients, of which 428 participated in the study; 217 were randomized to the intervention and 211 to care as usual (control).* ***Intervention:*** *The COSMOS intervention consisted of Communication, Systematic pain management, Medication reviews, Organization of activities, and Safety. During medication review, the nursing home physician evaluated treatment with colleagues systematically using the results from validated clinical assessments.* ***Measurements:*** *Mean changes from baseline to month 4 in the number of prescribed psychotropic drugs*

From the Centre for Elderly and Nursing Home Medicine, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway; Haraldsplass Deaconess Hospital, Bergen, Norway; Municipality of Bergen, Bergen, Norway; Section for Epidemiology and Medical Statistic, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway; Centre for Pharmacy/Department for Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway; Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway; and the NKS Olaviken Gerontopsychiatric Hospital, Bergen, Norway. Send correspondence and reprint requests to Marie H. Gedde M.D., Centre for Elderly and Nursing Home Medicine, University of Bergen, Kalfarveien 31, N-5020 Bergen, Norway. e-mail: marie.gedde@uib.no

https://doi.org/10.1016/j.jagp.2020.07.004

nursing homes
dementia

(antipsychotics, anxiolytics, hypnotics or sedatives, antidepressants, and antidementia drugs); Neuropsychiatric Inventory Nursing Home Version (NPI-NH) and Cornell Scale of Depression in Dementia (CSDD); Lawton and Brody's Physical Self Maintenance Scale (PSMS). ***Results:*** *Compared to control, the mean change in prescribed psychotropic drugs was reduced both in total and regular number, while mean changes in NPI-NH and CSDD scores did not differ between the groups. Mean change in PSMS showed improvement in the intervention group, and deterioration in the control group.* ***Conclusion:*** *Medication reviews using collegial mentoring and systematic clinical evaluation led to safe deprescribing, as the reductions in psychotropic drug use did not negatively affect BPSD, while ADL improved.* (Am J Geriatr Psychiatry 2021; 29:304–315)

OBJECTIVE

The introduction of psychotropic drugs in the 1950s revolutionized the understanding and treatment of severe psychiatric disorders, undoubtedly alleviating the symptom burden and improving daily functioning for persons with severe affective and psychotic disorders.[1] Today, these drugs are often used off-label, thus the use of psychotropic drugs for managing behavioral and psychological symptoms of dementia (BPSD) warrants special attention.[2–5] BPSD such as delusions, hallucinations, agitation, anxiety, and aberrant motor behavior are associated with poorer physical and cognitive functioning as symptoms persist and reoccur in the course of dementia.[2,6–8] Nonpharmacological approaches are the preferred first-line treatment, although severe and persistent symptoms may require pharmacological therapy.[2] However, treating BPSD with multiple psychotropic drugs like antipsychotics, anxiolytics, hypnotics or sedatives, and antidepressants often has limited therapeutic effect and compromises activities of daily living (ADL), and may even cause adverse, potentially fatal, side effects for elderly patients.[2,3,7–9]

In recent years, several clinical trials have aimed at optimization and reduction of psychotropic drug use in nursing home patients.[5,9–13] These interventions typically addressed antidepressant and antipsychotic drug use, with varying strategies, designs, and outcome measures. Concomitantly, the term deprescribing gradually developed and is now regarded as part of the prescription continuum for proactive, patient-centered therapy.[14] Reeve et al. defined deprescribing as "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes."[14] A recent systematic review on randomized controlled trials (RCTs) identified psychotropic drugs as the least responsive to deprescribing interventions among medications prescribed for chronic psychiatric and somatic conditions.[15] Further, it highlighted individualized drug recommendations and clinical assessments as necessary for the detection of symptom exacerbation and adverse effects to success with deprescribing. Even so, no previous RCT has explored the process of deprescribing as applied to all major groups of psychotropic drugs, while additionally evaluating the clinically relevant impact on BPSD and ADL.

Gulla et al. developed a method for interprofessional medication reviews using collegial mentoring and systematic clinical evaluation in nursing homes.[16] They implemented this strategy as a key component of the COSMOS trial, a multicomponent RCT, which also focused on communication, pain management, activities, and safety for nursing home patients.[17] In this study, we aim to investigate the effect of medication reviews on mean changes in the number of prescribed psychotropic drugs by using collegial mentoring and systematic clinical evaluation in the COSMOS trial, as well as explore if and how this approach is associated with changes in BPSD and ADL.

METHODS

This study presents secondary analyses of the 4-month multicenter, multicomponent, cluster-randomized, single-blinded controlled COSMOS trial.

Procedure

Intervention: The intervention consisted of five components, mirrored in the acronym COSMOS: Communication and advanced care planning, Systematic pain management, Medication reviews with collegial mentoring, Organization of activities adjusted to the individuals' need and preferences, and Safety. All the COSMOS components were implemented simultaneously in the nursing home units allocated to the intervention. The design, implementation process, and the primary outcome (Quality of Life) are described in detail elsewhere.[16–18]

The local nursing home physician performed the medication reviews together with a nurse and two research physicians (CG and BSH), who provided collegial mentoring. To structure the medication reviews, they utilized reports on validated assessment tools for the following: BPSD; ADL; pain; cognitive status and ability; well-being and quality of life; blood pressure; pulse; and body mass index.[16,17] The medical history including somatic and psychiatric diagnoses, as well as any laboratory test results requested by the nursing home physician, aided the revision of current drug use. A combination of the Norwegian Medical Agency's guidelines for medication reviews and the START or STOPP criteria, together with Duran et al.'s list of drugs with anticholinergic profiles available in Norway, assisted the medication reviews.[19–21] To detect drug interactions, nurses ran each patient's medication list through a database.[22] Nurses empowered patients and next of kin by incorporating their wishes and concerns into the medication reviews. The nursing home physician was responsible for medical treatment and any final decisions. An individual patient log tracked the clinical status and changes.

Control: Patients allocated to the control group received treatment as usual.

Sample

Nursing homes from eight municipalities of various size in Southern Norway were invited to participate in the COSMOS trial. The nursing home managers first authorized participation in the trial. Then a statistician randomized the units (clusters) of the participating nursing homes into an intervention and control group. Patients were recruited and included in the study from August 1, 2014 to March 15, 2015. Patients were followed for 4 months, with the last assessment on June 26, 2015. Patients aged ≥65 years with at least 2 weeks of residency in nursing homes were eligible. Exclusion criteria were schizophrenia and a life expectancy ≤ of 6 months.[17] Patients were lost at follow-up if they deceased or moved from the nursing home unit.

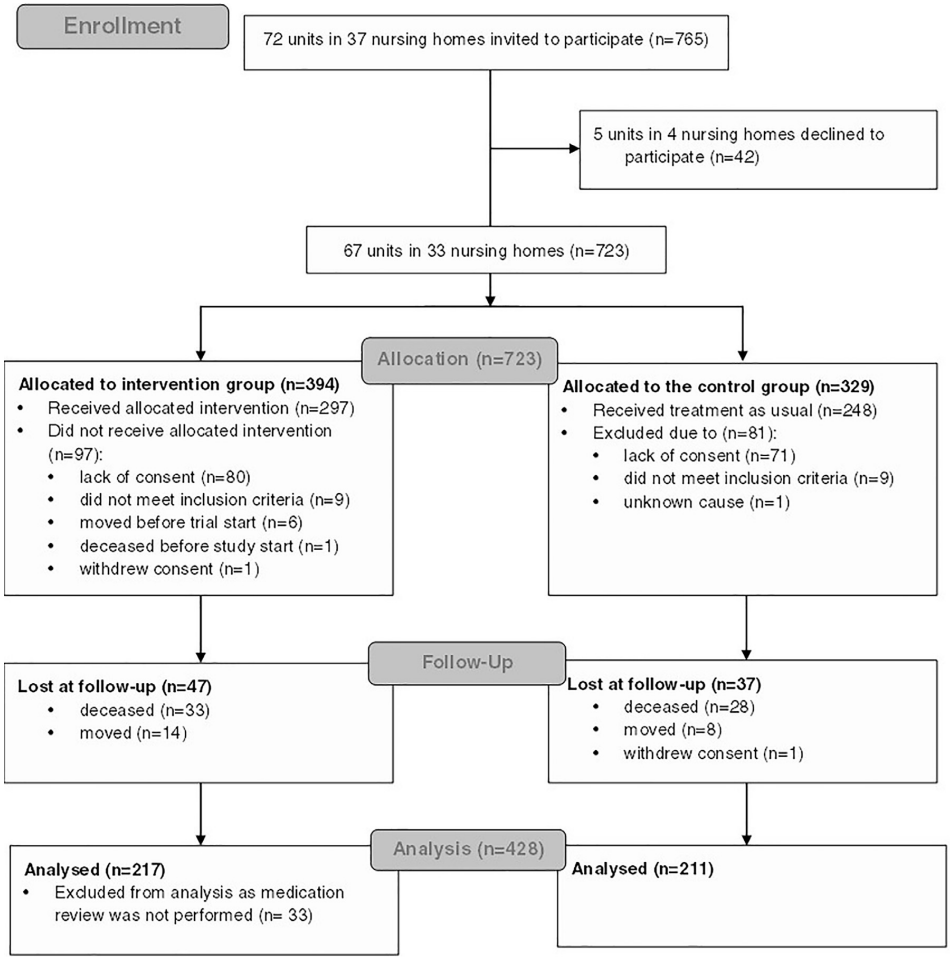
Of patients not lost to follow-up at 4 months, this study includes all controls and those patients in the intervention group who received medication reviews (Fig. 1: Flowchart). As shown in Figure 1, number of deceased patients were similar between the intervention and control group at 4 months follow-up.

Assessments

The primary outcome measure was mean change compared to baseline in numbers of prescribed psychotropic drugs, both in total and regularly at 4 months. The total number of prescribed drugs was the sum of regular and on-demand drug prescriptions of unique substances on the day of data collection. All drugs given on a set schedule counted as regularly prescribed drugs, and all others were considered on-demand. The following Anatomical Therapeutic Chemical Index classes qualified as psychotropic drugs: antipsychotics (N05A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D).[23]

The secondary outcome measures were mean changes in 1) BPSD estimated by the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) and the Cornell Scale for Depression in Dementia (CSDD), and 2) ADL evaluated by Physical Self Maintenance Scale (PSMS).[24–26] NPI-NH is a validated, proxy-rated instrument with high inter-rater reliability, determining the frequency (range: 1–4) and severity (range: 1–3) of 12 domains of BPSD over the preceding 4 weeks: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibitions, irritability, aberrant motorial behavior, sleep disturbances, and appetite changes.[24] The score for each domain is the frequency × severity product (range: 0–12), with domain scores ≥4 indicating symptoms of clinical relevance.[7] Adding the domain scores generates the NPI total score. CSDD is a proxy-rated instrument with good validity and reliability in screening persons with cognitive impairment or dementia for depression.[25] A total score of ≥8 indicates depression of clinical importance (range: 0–38). PSMS is valid and reliable for

FIGURE 1. Patient flow in the COSMOS trial; CONSORT 2010 flow diagram. CONSORT: Consolidated Standards of Reporting Standards; n: sample.



assessing each of the following six areas of ADL: feeding, dressing, grooming, physical ambulation, toileting, and showering.[26] Each area is rated on a five-point scale from full independence to full dependence (range: 6−30).

The *other variables* − age, sex, diagnoses by The International Classification of Primary Care, and the mini-mental status evaluation (MMSE) − were registered at baseline.[27,28] MMSE is a valid test of cognitive function assessing orientation, registration, attention, calculation, recalling, language manipulation, and the ability to follow commands (range: 0−30). A lower score indicates vaster impairment, of which ≤20 is characteristic of dementia.[27]

Statistical Analysis

We described baseline characteristics by frequency, percentage, mean, and standard deviation (SD).

Welch's unequal variance t test was used to compare the change between groups. In line with previous studies, we calculated the total scores without substitution for MMSE, NPI-NH, and CSDD when 80% of questions were answered and performed complete case analysis.[18] The level of significance was p value <0.05. We used multilevel mixed-effect negative binomial regression for modeling the number of prescribed psychotropic drugs over time for the intervention and control group. The analysis was carried out with time and unit as random effects to account for local variations in nursing home units. We performed all analysis with Stata or IC, release 16 (StataCorp LP, College Station, TX).

Ethics

The trial followed the recommendations of the Regional Committees for Medical and Health Ethics and Norwegian legislation concerning the matter of consent. All eligible patients and their next of kin or legal guardian received verbal and written information about the trial. If capable, the patient gave written, informed consent in direct conversation. If not, the next of kin or legal guardian provided presumed consent based on their determination of whether the patient, when he or she was able, would have agreed to participate. The Regional Committees for Medical and Health Ethics approved the trial (2013/1765), and ClinicalTrials.gov (NCT02238652) received the requisition prior to trial start.

RESULTS

Of the 723 nursing home patients enrolled in the COSMOS trial, we included in this study 428 patients not lost at the 4-month follow-up stratified into an intervention (N = 217) and control (N = 211) group (Fig. 1 and Table 1). Participants had a mean age of 86 (SD: 7.6), and 325 (76%) were female. The mean MMSE score was 12 (SD: 7.7), and 274 (64%) had a

TABLE 1. Baseline Characteristics for the Selected Sample of 428 Nursing Home Patients From the COSMOS Trial

	Intervention (N = 217)				Control (N = 211)			
	Mean	(SD)	n	(%)	Mean	(SD)	n	(%)
Demography								
Sex, female			165	(76)			160	(76)
Age	86.28	(7.95)			86.60	(7.21)		
Number of diagnoses	3.98	(3.03)			4.25	(3.37)		
Diagnosis of demented			141	(65)			133	(63)
MMSE	11.45	(7.47)	175	(81)	12.09	(7.93)	155	(73)
Drugs in general								
Total number	10.92	(4.60)	216	(100)	10.90	(4.69)	207	(98)
Regularly	7.49	(3.55)	214	(99)	7.63	(3.75)	207	(98)
On-demand	3.44	(2.28)	204	(94)	3.27	(2.00)	195	(92)
Psychotropic drugs								
Total number	2.18	(1.60)	187	(86)	2.24	(1.65)	175	(83)
Regularly	1.30	(1.19)	154	(71)	1.36	(1.24)	153	(73)
≥1 regularly	1.83	(1.01)	154	(71)	1.87	(1.07)	153	(73)
≥3 regularly	3.55	(0.62)	31	(14)	3.50	(0.77)	36	(17)
Classes regularly prescribed								
Antipsychotic drugs	0.19	(0.45)	37	(17)	0.13	(0.38)	25	(12)
Anxiolytic drugs	0.21	(0.43)	44	(20)	0.25	(0.50)	48	(23)
Hypnotic or sedative drugs	0.28	(0.49)	57	(26)	0.36	(0.55)	69	(33)
Antidepressant drugs	0.46	(0.63)	85	(39)	0.45	(0.58)	86	(41)
Antidementia drugs	0.15	(0.37)	32	(15)	0.16	(0.37)	34	(16)

N: sample; n: number of patients; SD: standard deviation; MMSE: mini-mental status evaluation; range 0−30, a lower score indicates vaster impairment of which ≤20 is characteristic for dementia. Diagnoses per the International Classification of Primary Care (ICPC). All drugs set in a schedule are regarded as regularly prescribed drugs; all other drugs were registered as on-demand. Drugs prescribed regularly plus those on-demand equals the total number of prescribed drugs. Psychotropic drugs: antipsychotics (N05A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D) according to the Anatomical Therapeutic Chemical Index (ATC).

TABLE 2. Secondary Outcome Measures at Baseline for the Selected Sample of 428 Nursing Home Patients From the COSMOS Trial

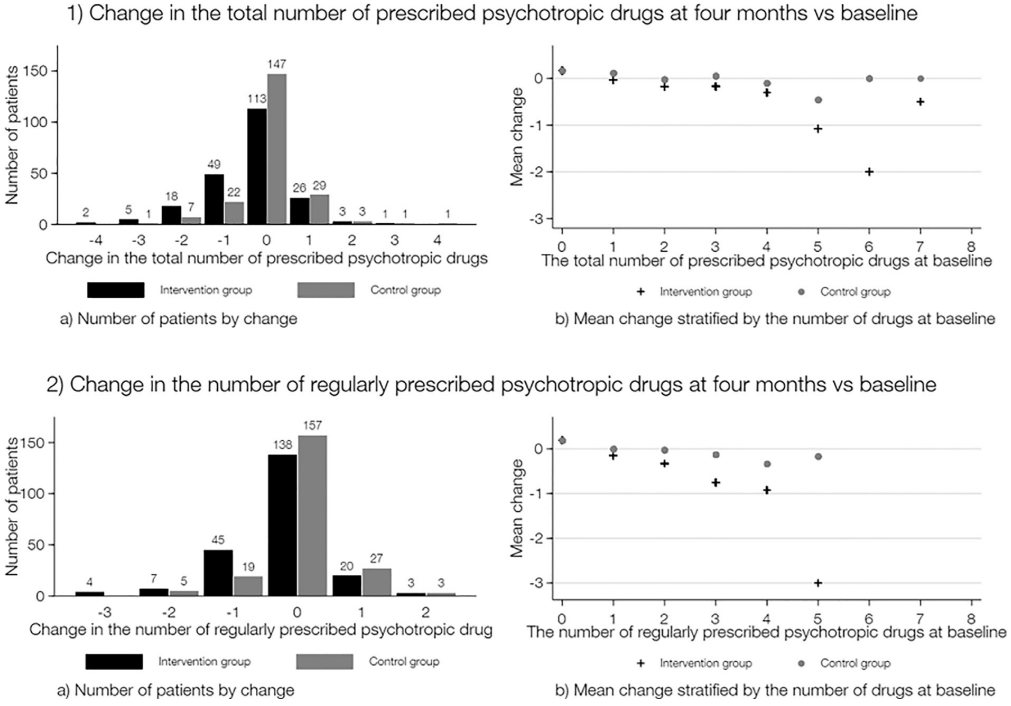
	Intervention (N = 217)			Control (N = 211)		
	Mean	(SD)	n	Mean	(SD)	n
Behavioral and psychological symptoms of dementia						
NPI-NH						
Total score	17.49	(18.97)	215	17.61	(21.12)	204
Domains						
Delusions	1.37	(2.88)	216	1.87	(3.52)	204
Hallucinations	0.69	(2.05)	216	0.86	(2.54)	206
Agitation	2.15	(3.44)	213	1.89	(3.43)	204
Depression	2.49	(3.67)	214	1.80	(3.21)	204
Anxiety	2.20	(3.84)	214	2.35	(3.82)	205
Euphoria	0.35	(1.46)	214	0.39	(1.55)	205
Apathy	1.26	(2.65)	213	1.00	(2.24)	203
Disinhibitions	1.25	(2.79)	216	1.31	(2.84)	204
Irritability	2.57	(3.45)	214	2.77	(3.82)	205
Aberrant motor behavior	0.85	(2.44)	213	1.20	(3.14)	205
Sleep disturbances	1.61	(3.18)	215	1.65	(3.06)	204
Appetite changes	1.26	(2.65)	213	1.00	(2.24)	203
≥1 domain of clinical relevance, n (%)	154	(71)	217	134	(64)	211
CSDD						
Total score	7.30	(6.33)	214	7.56	(6.40)	205
Total score of clinical relevance, n (%)	85	(39)	214	90	(43)	205
Level of functioning						
PSMS total score	17.25	(5.14)	216	16.43	(5.49)	206
Toileting	2.90	(1.57)	216	2.59	(1.47)	206
Feeding	1.71	(1.09)	216	1.70	(1.06)	206
Dressing	3.07	(1.17)	216	2.96	(1.30)	206
Grooming	3.39	(0.97)	216	3.25	(1.11)	206
Physical ambulation	2.79	(0.93)	216	2.77	(0.88)	206
Showering	3.38	(0.98)	216	3.19	(1.02)	205

N: sample; n: number of patients; SD: standard deviation; NPI-NH: 12 item Neuropsychiatric Inventory Nursing Home Version, total scores range 0−144, domain scores range 0−12; scores ≥4 are considered of clinical relevance; CSDD: Cornell Scale of Depression in Dementia, total scores range 0−38, scores ≥8 are considered of clinical relevance; PSMS, Lawton and Brody's Physical Self Maintenance Scale, range 6−30, higher scores indicate a lower level of functioning in activities of daily living.

formal diagnosis of dementia. Three hundred and seven (72%) patients used psychotropic drugs regularly, and 67 (16%) used three or more, while 268 (63%) received psychotropic drugs on-demand. Antidepressants were the most frequent regularly prescribed psychotropic drug (40%; Table 1), while anxiolytics were most often prescribed on-demand (48%, data not shown). Clinically relevant BPSD assessed by NPI-NH were present for 288 (67%) patients, with the highest mean scores occurring in the domains of irritability and anxiety (Table 2). According to the CSDD, 175 (41%) met the criteria for clinical relevant depression (Table 2). The overall mean PSMS score was 17 (SD: 5.3).

From baseline to month 4, 74 (34%) patients in the intervention group discontinued at least one prescribed psychotropic drug, given either regularly or on-demand; the corresponding number was 30 (14%) among those randomized into the control group (Panel 1a, Fig. 2). Similarly, 56 (26%) patients in the intervention group and 24 (11%) in the control group discontinued any regularly prescribed psychotropic drugs (Panel 2a, Fig. 2). Panel 1b and 2b of Figure 2 visualizes the mean changes in psychotropic drug use stratified by the number of prescribed psychotropics in the intervention and control groups. Table 3 quantifies these reductions, showing that the number of discontinued drugs in the intervention group increased by higher numbers of psychotropic drugs at baseline. Patients in the intervention group who were regularly prescribed three or more psychotropic drugs at baseline (n = 31) had a significantly higher mean reduction compared to the control group (n = 36; Table 3). Compared to the control group, the regular use of hypnotics or sedatives (N05C) and antidepressant drugs (N06A) were reduced during the intervention (Table 3), while no difference in mean

FIGURE 2. Changes in prescribed psychotropic drugs at 4 months versus baseline for the selected sample of 428 nursing home patients from the COSMOS trial. Panel 1 illustrates changes in the total number of prescribed psychotropic drugs. Panel 2 illustrates changes in regularly prescribed psychotropic drugs. Mean changes stratified by the number of prescribed psychotropic drugs at baseline; (1b) the total number and (2b) in regular use.



change for antipsychotics (N05A), anxiolytics (N05B), and antidementia drugs (N06D) were found.

The mean change in total NPI-NH score did not differ between the intervention group and the control group, nor did the domain scores or the mean change in the CSDD total score (Table 3). Level of functioning in ADL, measured by the PSMS total score at month 4, improved overall for the intervention group and worsened in the control group, yet none of the discrete items differed (Table 3).

We performed a multilevel mixed-effect negative binomial regression with random effects of time and nursing home clusters and found no association between time and cluster variations regarding prescribed psychotropic drugs by total number or regularly prescription (data not shown). Defining antiepileptic drugs (N03A)[23] as psychotropic drugs increased the number of patients using psychotropic drugs at baseline by three persons, in both the intervention and control group. This led to no alterations in the primary and secondary outcome measures (data not shown). As a measure of adverse events, we conducted a post hoc analysis, showing no differences in hospitalizations between the groups at follow-up (data not shown).

DISCUSSION

Our medication review based on collegial mentoring and systematic clinical evaluation reduced the prescription of psychotropic drugs in nursing home patients without any deterioration in their behavioral

TABLE 3. Changes Within the Intervention and Control Group at 4 Months Versus Baseline for the Selected Sample of 428 Nursing Home Patients From the COSMOS Trial

	Four Months Versus Baseline							
	Intervention (N = 217)			Control (N = 211)				
	Mean	(SD)	n	Mean	(SD)	n	df	p Value*
Drugs in general								
Total number	-1.31	(2.90)	217	-0.31	(1.92)	211	418	<0.001
Regularly	-0.99	(2.32)	217	-0.30	(1.64)	211	418	<0.001
Psychotropic drugs								
Total number	-0.34	(1.01)	217	0.01	(0.77)	211	426	<0.001
Regularly	-0.21	(0.78)	217	0.02	(0.61)	211	426	<0.001
≥1 regularly	-0.37	(0.82)	154	-0.05	(0.65)	153	305	<0.001
≥3 regularly	-0.97	(1.05)	31	-0.17	(0.65)	36	65	<0.001
Classes regularly prescribed								
Antipsychotic drugs	-0.02	(0.33)	217	0.02	(0.23)	211	426	0.087
Anxiolytic drugs	-0.01	(0.33)	217	-0.01	(0.32)	211	426	0.874
Hypnotic or sedative drugs	-0.03	(0.39)	217	0.06	(0.33)	211	426	0.011
Antidepressants drugs	-0.11	(0.46)	217	0.02	(0.36)	211	426	0.041
Antidementia drugs	-0.04	(0.27)	217	-0.02	(0.18)	211	426	0.555
Behavioral and psychological symptoms of demented								
NPI-NH								
Total score	-3.41	(20.63)	212	-0.90	(17.07)	200	410	0.180
Domains								
Delusions	-0.31	(3.28)	213	-0.10	(3.24)	201	412	0.532
Hallucinations	-0.02	(2.21)	215	0.00	(2.32)	203	416	0.899
Agitation	-0.75	(3.49)	212	-0.36	(3.22)	201	411	0.242
Depression	-0.63	(4.10)	209	-0.19	(2.71)	199	406	0.203
Anxiety	-0.23	(3.97)	209	-0.43	(3.49)	201	408	0.592
Euphoria	-0.11	(1.48)	211	0.20	(1.88)	202	411	0.058
Apathy	-0.30	(3.26)	211	0.14	(2.41)	198	407	0.124
Disinhibitions	-0.21	(2.94)	215	0.14	(2.93)	200	413	0.226
Irritability	-0.68	(3.88)	210	-0.31	(3.31)	201	409	0.303
Aberrant motor behavior	-0.08	(2.60)	211	-0.06	(3.37)	202	411	0.943
Sleep disturbances	-0.25	(2.92)	215	-0.25	(2.82)	201	414	0.993
Appetite changes	0.18	(3.28)	212	0.32	(2.18)	198	408	0.615
CSDD								
Total score	-0.18	(6.05)	213	-0.14	(5.66)	202	413	0.945
Level of functioning								
PSMS total score	-0.13	(4.22)	216	0.73	(3.45)	204	418	0.023
Toileting	-0.01	(1.33)	216	0.15	(1.31)	203	417	0.196
Feeding	0.12	(0.95)	216	0.17	(0.76)	203	417	0.501
Dressing	0.01	(1.10)	216	0.20	(0.90)	203	417	0.058
Grooming	-0.04	(1.00)	214	0.13	(0.84)	201	413	0.061
Physical ambulation	0.02	(0.86)	216	0.13	(0.74)	204	418	0.165
Showering	-0.18	(1.12)	216	0.00	(1.06)	203	417	0.091

N: sample; n: number of patients; SD: standard deviation; df: degrees of freedom; NPI-NH: 12 item Neuropsychiatric Inventory Nursing Home Version, total scores range 0–144, domain scores range 0–12; CSDD: Cornell Scale of Depression in Dementia, total score range 0–38; PSMS: Lawton and Brody's Physical Self Maintenance Scale, range 6–30, higher scores indicate a lower level of functioning in activities of daily living.

*Welch's unequal variance t test was used to compare the change between groups. All drugs set in a schedule are regarded as regularly prescribed drugs, all other drugs were registered as on-demand. Adding drugs regularly prescribed drugs to on-demand equals the total number of prescribed drugs. Psychotropic drugs: antipsychotics (N05A), anxiolytics (N05B), hypnotics or sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D) according to the Anatomical Therapeutic Chemical Index (ATC).

disturbances. Highest reductions in number of psychotropic drugs were found among patients who received several at baseline. Most frequently, antidepressants and sedatives were reduced, leading to a significant clinical improvement in the patients' physical function. Even though we acknowledge that psychotropic drugs are beneficial for some, our findings emphasize that *less* inappropriate psychotropic drug prescription has the potential for *more* and better physical function in nursing home patients.

We report an overall reduction in use of psychotropic drugs, which did not lead to compensatory increased use of psychotropic drugs on demand. A noncontrolled study conducted psychotropic prescription reviews solely based on medical records in aged care facilities, resulting in a 24% discontinuation of antipsychotic drugs and benzodiazepines.[11] This resembles our finding of a modest reduction in regularly prescribed psychotropic drugs after a 4-month follow-up. However, joint reviews integrating measures of cognitive and physical impairment in a pre- or postintervention trial greatly reduced persistent use of the major classes of psychotropic drugs in institutionalized patients with dementia.[12] We found the highest reductions among patients receiving several psychotropic drugs and those classes of drugs most often prescribed in nursing homes today, namely antidepressants and hypnotics or sedatives.[3] The major attention given to the possible overuse of, in particular, antipsychotic medication in nursing homes the last decade in many ways paved the way for the development of the COSMOS intervention.[3,29] As such, relatively few patients used these drugs at baseline (Table 1), partly explaining the lack of significant reductions in use of antipsychotic medication.

This is the first RCT that reports on BPSD concerning the process of deprescribing more than two classes of psychotropic drugs in a nursing home sample. Despite reductions in overall psychotropic drug use, we found no emerging difference in BPSD between the intervention and control group, supported by previous reports indicating that separate classes of psychotropic drugs can be safely withdrawn if done cautiously.[15,30] In several cohorts, multi-psychotropic drug use was associated with severe BPSD, illustrating the symptom complexity and therapeutic shortcomings of available medication.[3] The highly remitting and relapsing course of BPSD further complicates interpretations of the cause and effects of these drugs, whose side effects such as latency, apathy, and anxiety might also mimic BPSD.[2,7,31] The randomized CATIE-AD trial found similar symptom-trajectories of BPSD, irrespective of treatment with second-generation antipsychotic drugs among 371 patients with Alzheimer's dementia.[32] The retrospective reporting from the HALT study found that antipsychotic medication were prescribed as a maintenance treatment, despite absence of BPSD, and that standardized medication review alone were insufficient to withdraw prolonged administration of antipsychotics in long-term care.[10] However, the DESEP trial induced exacerbating depressive symptoms following an intervention exclusively comprising randomized discontinuation of antidepressants for nursing home patients with BPSD and dementia.[9] In contrast, the WHELD trial randomized nursing home patients into antipsychotic review alone or in combination with social and physical exercise.[5] The results showed that BPSD increased in the group that only received medication reviews, underlining the importance of nonpharmacological interventions implemented alongside medication reviews. In our trial, all the additional COSMOS components − communication and advanced care planning, pain management, activities, and focus on safety − likely contributed to the stabilization of BPSD following medication reviews.[2,5,15] Differing designs and populations obviously challenge direct comparisons of interventions solely reviewing medication contrasting those additionally including nonpharmacological elements. Nonetheless, these reports consolidate the COSMOS strategy for individualized care by incorporating assessments of BPSD and identifying both underlying medical issues and unmet needs in combination with nonpharmacological approaches, balancing the twin traps of overtreatment and therapeutic nihilism in nursing home medicine.[2,30,33,34]

During this 4-month study, the patients in the intervention group improved in ADL, whereas the dependency of the control group was aggravated. Our findings are encouraging, as the loss of ADL skills in dementia are regarded as irreversible.[35] A range of factors including progression of cognitive impairment, BPSD, and psychotropic drugs condition the loss of ADL skills, likely increasing the risk of exacerbating BPSD.[8,31,35] This can, in a worst case scenario, initiate a self-enforcing circle of accumulating and lingering psychotropic drug therapy, again aggravating dependence in ADL.[3,8,10] Few studies have explored the association between pharmacological treatment of BPSD and ADL. Some have found advantageous effects, particular concerning the use of antidepressants, although it is debated whether this effect is of clinical relevance.[36,37] Anxiolytic drugs, however, substantially impaired ADL, despite improvement in BPSD among 89 patients with dementia admitted to acute psychogeriatric inpatient wards.[38] Further, antipsychotics, in addition to

anxiolytics, were associated with functional decline in ADL for 236 home-dwelling elderly with dementia.[39] Interestingly, Global Assessment of Functioning score improved by electroconvulsive treatment in agitated elderly patients with dementia, while both BPSD and psychotropic drug use decreased.[40] Nevertheless, being a tool for overall assessment of functioning, the Global Assessment of Functioning score describes how well the patient meets various problems-in-living and does not equate to ADL per se. That being said, their findings corroborate a more dynamic understanding of ADL in dementia as reversible through both pharmacological and nonpharmacological interventions.

A principal strength of the COSMOS trial is the rigorous method for comprehensive medication review with a multidisciplinary, systematic approach that utilizes validated assessments.[16] Physicians working in municipal nursing homes, the majority being general practitioners, were recruited to the trial and placed in charge of undertaking the medication reviews and further treatment. This suggests that the method can be adapted in other first-line clinical settings, not determinant on specialist qualifications. Further, the COSMOS trial is the largest RCT conducted in an unselected sample of nursing home patients, yielding high generalizability of our findings. The large sample size allowed for the investigation of several classes of psychotropic drugs prescribed regularly and on-demand, including their associations with clinically relevant outcomes, such as BPSD and physical functioning.

Our findings should be interpreted in light of some limitations. This was a completers only analysis limiting the generalizability to nondeceased patients. Some of the physicians responsible for the systematic medication reviews worked in both the intervention and control units. Therefore, the principles for medication reviews could have contaminated the outcomes of the control group, possibly reducing the difference in change in psychotropic drugs between our two comparison groups. We also expect a reduced intervention effect caused by treatment that was started during admission to hospital or prescribed by external physicians not familiar with the COSMOS trial, as indications and durations of therapy were not registered. Some aspects of the COSMOS intervention are likely less feasible in clinical practice, due to resource demanding nonpharmacological components and logistics, such as researchers mentoring the nursing home physicians in performing medication reviews.[16] Due to multiple testing, the chance of false-positive findings increase. Further, we did not consider defined daily doses of the various classes of psychotropic drugs, nor other influencing factors on BPSD such as pain assessments and analgesics. As data on BPSD and ADL had to be assessed by the caregivers most proximate to the patients being the once also delivering the intervention, the single-blinded design can increase the risk of reporting bias.

CONCLUSION

Medication review with collegial mentoring based on systematic clinical evaluation reduced the prescription of psychotropic drugs in nursing home patients without deterioration in BPSD, yet independence in ADL improved. This illustrates that less is actually more concerning psychotropic drug use and overall functioning. Our procedure represents valuable decision-making support for the clinician to establish and maintain appropriate psychotropic prescribing in nursing homes.

AUTHOR CONTRIBUTIONS

MHG led the conception of work and analyses, as well as the interpretation of data for publication and the writing of the manuscript. LIB, BSH, JM, MN, and RLSK contributed to the design and the writing of the manuscript, namely preparation and critical revision. JM supervised the analyses. BSH was primary investigator for the COSMOS trial. All authors have read and approved the final version for publication.

The Research Council of Norway (*Sponsor's Protocol Code*: 222113) *and* Rebekka Ege Hegermann's Foundation *sponsored the trial. The* Research Council of Norway *also grants positions for MHG, JM, and LIB (Sponsor's Protocol Code*: 273581). *The Norwegian Government and the G.C. Rieber Foundation support the Centre for Elderly and Nursing Home Medicine, University of Bergen*. The sponsors had no influence on the trial concept and design, recruitment of patients, analyses and interpretation of data, or preparation of the manuscript.

DISCLOSURE

The authors report no conflicts with any product mentioned or concepts discussed in this article.

References

1. Ban TA: Pharmacotherapy of mental illness—a historical analysis. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25:709–727
2. Bessey LJ, Walaszek A: Management of behavioral and psychological symptoms of dementia. Curr Psychiatry Rep 2019; 21:66
3. 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
4. Helvik A-S, JŠ Benth, Wu B, et al: Persistent use of psychotropic drugs in nursing home residents in Norway. BMC Geriatr 2017; 17:52
5. Ballard C, Orrell M, YongZhong S, et al: Impact of antipsychotic review and nonpharmacological intervention on antipsychotic use, neuropsychiatric symptoms, and mortality in people with dementia living in nursing homes: a factorial cluster-randomized controlled trial by the well-being and health for people with dementia (WHELD) program. Am J Psychiatry 2016; 173:3
6. Burhanullah MH, Tschanz JT, Peters ME, et al: Neuropsychiatric symptoms as risk factors for cognitive decline in clinically normal older adults: the cache county study. Am J Geriatr Psychiatry 2020; 28:64–71
7. Vik-Mo AO, Giil LM, Borda MG, et al: The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. Br J Psychiatry 2020; 216:43–48
8. Helvik AS, Hogseth LD, Bergh S, et al: A 36-month follow-up of decline in activities of daily living in individuals receiving domiciliary care. BMC Geriatr 2015; 15:47
9. Bergh S, Selbæk 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
10. Harrison F, Cations M, Jessop T, et al: Prolonged use of antipsychotic medications in long-term aged care in Australia: a snapshot from the HALT project. Int Psychogeriatr 2020: 1–11
11. Westbury JL, Gee P, Ling T, et al: RedUSe: reducing antipsychotic and benzodiazepine prescribing in residential aged care facilities. Med J Aust 2018; 208:398–403
12. Mesquida MM, Casas MT, Sisó AF, et al: Consensus and evidence-based medication review to optimize and potentially reduce psychotropic drug prescription in institutionalized dementia patients. BMC Geriatr 2019; 19:7
13. van der Spek K, Koopmans RT, Smalbrugge M, et al: The effect of biannual medication reviews on the appropriateness of psychotropic drug use for neuropsychiatric symptoms in patients with dementia: a randomised controlled trial. Age Ageing 2018; 47:430–437
14. Reeve E, Gnjidic D, Long J, et al: A systematic review of the emerging definition of 'deprescribing'with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol 2015; 80:1254–1268
15. Dills H, Shah K, Messinger-Rapport B, et al: Deprescribing medications for chronic diseases Management in primary care settings: a systematic review of randomized controlled trials. J Am Med Dir Assoc 2018; 19:923–935
16. Gulla C, Flo E, Kjome RLS, et al: Implementing a novel strategy for interprofessional medication review using collegial mentoring and systematic clinical evaluation in nursing homes (COSMOS). BMC Geriatr 2019; 19:130
17. 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
18. Husebo BS, Ballard C, Aarsland D, et al: The effect of a multicomponent intervention on quality of life in residents of nursing homes: a randomized controlled trial (COSMOS). J Am Med Dir Assoc 2019; 20:330–339
19. Duran CE, Azermai M, Vander Stichele RH: Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol 2013; 69:1485–1496
20. 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; 44:2013–2018
21. Norwegian Medicines Agency, The Norwegian Directorate of Health: Sjekkliste for legemiddelgjennomgang (check list for medication meview) [Web site]. November 15 2016, Available at: https://www.helsebiblioteket.no/251793.cms. Accessed October 10, 2019, 2016
22. Interaksjoner.no [database online], Bergen, The Norwegian Medicines Agency, 2014
23. ATC/DDD Index [database online], Oslo, WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health, 2015.
24. Selbaek G, Kirkevold O, Sommer OH, et al: The reliability and validity of the Norwegian version of the neuropsychiatric inventory, nursing home version (NPI-NH). Int Psychogeriatr 2008; 20:1–9
25. Barca ML, Engedal K, Selbæk G: A reliability and validity study of the cornell scale among elderly inpatients, using various clinical criteria. Dement Geriatr Cogn Disord 2010; 29:438–447
26. Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–186
27. Folstein MF, Folstein SE, McHugh PR: Mini-mental state — practical method for grading cognitive state of patients for clinician. J Psychiatr Res 1975; 12:189–198
28. Lamberts H, Wood M, Hofmans-Okkes I: The International Classification of Primary Care in the European Community: With a Multi-Language Layer. Oxford University Press, 1993
29. Janus SI, van Manen JG, IJzerman MJ, et al: Psychotropic drug prescriptions in Western European nursing homes. Int Psychogeriatr 2016; 28:1775–1790
30. Harrison SL, Cations M, Jessop T, et al: Approaches to deprescribing psychotropic medications for changed behaviours in long-term care residents living with dementia. Drugs Aging 2019; 36:125–136
31. Tveito M, Correll CU, Bramness JG, et al: Correlates of major medication side effects interfering with daily performance: results from a cross-sectional cohort study of older psychiatric patients. Int Psychogeriatr 2016; 28:331–340
32. Ozawa C, Roberts R, Yoshida K, et al: Placebo effects in the treatment of noncognitive symptoms of Alzheimer's disease: Analysis of the CATIE-AD data. J Clin Psychiatry 2017; 78:e1204–e1210
33. 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; 22:708–717
34. Ferreira AR, Simões MR, Moreira E, et al: Modifiable factors associated with neuropsychiatric symptoms in nursing homes: the

impact of unmet needs and psychotropic drugs. Arch Gerontol Geriatr 2020; 86:103919
35. Mlinac ME, Feng MC: Assessment of activities of daily living, self-care, and independence. Arch Clin Neuropsychol 2016; 31:506–516
36. Luo H, Tang JY, Wong GH, et al: The effect of depressive symptoms and antidepressant use on subsequent physical decline and number of hospitalizations in nursing home residents: a 9-year longitudinal study. J Am Med Dir Assoc 2015; 16:1048–1054
37. Dutcher SK, Rattinger GB, Langenberg P, et al: Effect of medications on physical function and cognition in nursing home residents with dementia. J Am Geriatr Soc 2014; 62:1046–1055
38. Alanen H-M, Pitkänen A, Suontaka-Jamalainen K, et al: Acute psychogeriatric inpatient treatment improves neuropsychiatric symptoms but impairs the level of functioning in patients with dementia. Dement Geriatr Cogn Disord 2015; 40:290–296
39. Törmälehto S, Martikainen J, Bell JS, et al: Use of psychotropic medications in relation to neuropsychiatric symptoms, cognition and functional performance in Alzheimer's disease over a three-year period: Kuopio ALSOVA study. Int Psychogeriatr 2017; 29:1723–1733
40. Hermida AP, Tang Y-l, Glass O, et al: Efficacy and safety of ECT for behavioral and psychological symptoms of dementia (BPSD): a retrospective chart review. Am J Geriatr Psychiatry 2020; 28:157–163

Paper II

Gedde MH, Husebo BS, Mannseth J, Naik M, Selbaek G, Vislapuu M, Berge LI: The impact of medication reviews by general practitioners on psychotropic drug use and behavioral and psychological symptoms in home-dwelling people with dementia: Results from the multicomponent cluster-randomized controlled LIVE@Home.Path trial. BMC Med 2022;20:186.

Gedde *et al. BMC Medicine* (2022) 20:186
https://doi.org/10.1186/s12916-022-02382-5

BMC Medicine

RESEARCH ARTICLE Open Access

The impact of medication reviews by general practitioners on psychotropic drug use and behavioral and psychological symptoms in home-dwelling people with dementia: results from the multicomponent cluster randomized controlled LIVE@Home.Path trial

Marie H. Gedde[1,2*], Bettina S. Husebo[1,3], Janne Mannseth[4], Mala Naik[2,5], Geir Selbaek[6,7,8], Maarja Vislapuu[1] and Line Iden Berge[1,9]

Abstract

Background: There is limited knowledge regarding the process of deprescribing psychotropic drugs to people with dementia (PwD) conducted by general practitioners (GP). We investigated the impact of a multicomponent intervention, emphasizing medication reviews, on psychotropic drugs and behavioral and psychological symptoms (BPSD) in home-dwelling PwD and quantified change in patient-GP communication evaluated by their informal caregivers.

Methods: LIVE@Home.Path is a stepped-wedge closed-cohort cluster randomized controlled trial for people with mild to moderate dementia aged ≥65 and their informal caregivers (dyads) in Norway. Complementary to health care as usual (control condition), municipal coordinators implemented the multicomponent LIVE intervention: Learning, Innovation, Volunteer support, and Empowerment (including medication review by the PwD's regular GPs). Block-randomization was used to allocate dyads in three groups receiving the intervention sequentially in periods of 6 months duration. Prepandemic data from the first period is reported, resulting in a 1:2 intervention-to-control ratio. Primary outcome was change in psychotropic drug use. Secondary outcomes were changes in BPSD by Neuropsychiatric Inventory and Cornell Scale of Depression in Dementia and patient-GP communication by an adaption of the Clinical Global Impression of Change.

Results: Four hundred thirty-eight dyads were screened, 280 included, and 237 participated at 6 months (intervention group *n*=67; control condition *n*=170). At baseline, 63% used psychotropic medication regularly: antidementia drugs (47%), antidepressants (13%), hypnotics/sedatives (13%), antipsychotics (5%), and anxiolytics (2%). At 6 months, medication reviews were more frequently conducted in the intervention group compared to control (66% vs 42%, *P*=0.001). We found no differences regarding a change in drug use and BPSD. Patient-GP communication enhanced in the intervention group (mean score 0.95 [standard deviation 1.68] vs 0.41 [1.34], *P*=0.022). In the intervention

*Correspondence: marie.gedde@uib.no

[2] Haraldsplass Deaconess Hospital, Bergen, Norway
Full list of author information is available at the end of the article

group, control group, and overall sample, the informal caregivers of those who had their medications reviewed reported improved patient-GP communication compared to those who did not.

Conclusions: Change in psychotropic drug use and BPSD did not differ, even though patient-GP communication improved with medication reviews. Restricted psychotropic drug use among PwD likely reflects more judicious prescribing practices in recent years. Nevertheless, medication reviews could be cultivated to optimize pharmacologic treatment for this complex population.

Trial registration: ClinicalTrials.gov: NCT04043364; registered 15/03/2019.

Keywords: Medication review, Deprescribing, Multicomponent intervention, Psychotropic drugs, Behavioral and psychological symptoms of dementia, Neuropsychiatric symptoms, Dementia, Home-dwelling, LIVE@Home.Path

Background

The number of people with dementia (PwD) is growing dramatically, and the increased disease burden is impacting health care services and societies worldwide [1]. Dementia is a chronic syndrome characterized by progressive cognitive impairments that interfere with daily living, usually accompanied by behavioral and psychological symptoms (BPSD) [1, 2]. BPSD consist of changes in behavior, mood, thoughts, and perception that can be very stressful for the individual and their informal caregivers (family members) [2]. Furthermore, BPSD are associated with poorer cognitive and everyday functioning, which can increase the risk of early transfer from home to permanent nursing home care and reduce life expectancy [3, 4].

Non-pharmacological interventions are recommended as the first-line approach to target BPSD [5, 6]. Although the effects of antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, and antidementia drugs are modest, these medications may be relegated as a second-line treatment when severe symptoms persist [5, 6]. Moreover, psychotropic drugs may increase the risk of functional decline, strokes, falls, and even early death in this population [7, 8].

The combination and long-term use of these drugs warrant special attention. In a population-based sample from England (n=27,090), Richardson et al. (2020) documented that PwD prescribed with Z-hypnotics were more likely to also receive antipsychotics and antidepressants [9]. Similarly, an Italian registry study (n=24,735) demonstrated that community-dwelling PwD using antidepressants or antidementia drugs had higher odds of being prescribed antipsychotic medication [10]. Even more, 44% of those receiving antipsychotics were treated longer than was recommended by guidelines [10]. Another registry study from Norway (n=22,119) found that indications for use and in-home medication routines for elderly were seldom revised as large-quantum packages of sedatives and hypnotics were frequently issued by general practitioners (GPs) during indirect patient contacts (e.g., office-visit without consultation with the GP or contact by telephone) [11]. However, this study did not specify if the participants were diagnosed with dementia [11]. Data from the REDIC-NH study, collected in Norway between 2012 and 2014, revealed that 68% of PwD (n=696) used at least one psychotropic drug at nursing home admission [12]. These consisted of antipsychotics 14%, anxiolytics 17%, hypnotics and sedatives 22%, antidepressants 31%, and antidementia drugs 31% [12]. The frequent use at nursing home admission underlines the need to evaluate the ongoing use of psychotropic drugs in PwD while still residing at home [12]. This is particularly important as approximately 70% of the PwD in Norway are home-dwelling [13].

A recent expert opinion concludes that the next step in the deprescribing field should tailor interventions for home-dwelling PwD while also involving their informal caregivers to identify preferences for medication use and overall health [14]. Such interventions might be considered complex due to the permitted degree of tailoring or inherent properties of the intervention (e.g., multiple and interacting components) [15]. Even though complex interventions are essential for changing clinical practices [15], the best evidence to support deprescribing is for high-risk medications among PwD living in long-term care facilities [14]. For instance, the WHELD trial demonstrated that antipsychotic drug withdrawal was most beneficial for BPSD and mortality for PwD living in nursing homes when social interactions were promoted in parallel [16]. Similarly, physician-led medication reviews embedded in the multicomponent COSMOS trial reduced psychotropic drug use without compromising BPSD, and additionally improved communication between health personnel, nursing home patients, and their relatives [17, 18]. Additionally, communication is an integral part of the work of all Norwegian general practitioners (GPs) in providing continuity in medical care to their enlisted home-dwelling patients. On indication, GPs are obliged to conduct medication reviews among PwD every 6–12 months [6]. Still, we lack knowledge on to which extent they consistently review their medications, as well as the impact of medication reviews on

psychotropic drug use. In this substudy, we investigate the impact of a multicomponent intervention emphasizing medication review on changes in psychotropic drug use and BPSD in home-dwelling PwD and their communication with their GPs.

We hypothesize that:

1) The multicomponent intervention emphasizing GP conducted medication reviews will reduce psychotropic drug use.
2) This deprescribing process will not change BPSD but improve patient-GP communication.

Methods

Design

This is a substudy of LIVE@Home.Path: a multicenter, stepped-wedge cluster randomized controlled trial investigating if a multicomponent intervention for dyads of home-dwelling PwD and informal caregivers (family members) improves resource utilization and caregiver burden in dementia care [19]. With 80% power and 5% significance level allowing for 20% loss to follow-up, a sample of 315 dyads was required to detect a difference of 7 care hours per week for the primary outcome care time assessed with Resource Utilization in Dementia [20], based on the assumption that the informal caregivers provided 46 care hours weekly [21]. This stepped-wedge trial used a closed-cohort design, implying that all dyads were recruited before randomization [22]. We used block randomization to allocate dyads in three intervention groups (Group 1, Group 2, Group 3), which were scheduled to receive the multicomponent intervention sequentially in periods of 6 months duration during the 24-month trial (Fig. 1). While the intervention groups were waiting to receive the intervention, they served as controls receiving health care as usual. Dyads were blinded to allocation until their designated coordinator contacted them to receive the intervention, while the nature of the intervention prevented blinding of care providers and dyads. The trial was conducted in Bergen, Bærum, and Kristiansand municipality, Norway, 2019–2021. The first 6-month period was completed in March 2020 as the COVID-19 pandemic temporarily halted the trial protocol (Fig. 1) [23]. Therefore, this substudy includes all dyads completing the first 6-month period, the dyads randomized to Group 1 constitute the intervention group and the dyads randomized to Groups 2 and 3 constitute the control group (Fig. 2).

Intervention

LIVE is an acronym for the multicomponent intervention in which a coordinator facilitated Learning, Innovation, Volunteer support, and Empowerment emphasizing medication reviews. Table 1 outlines the

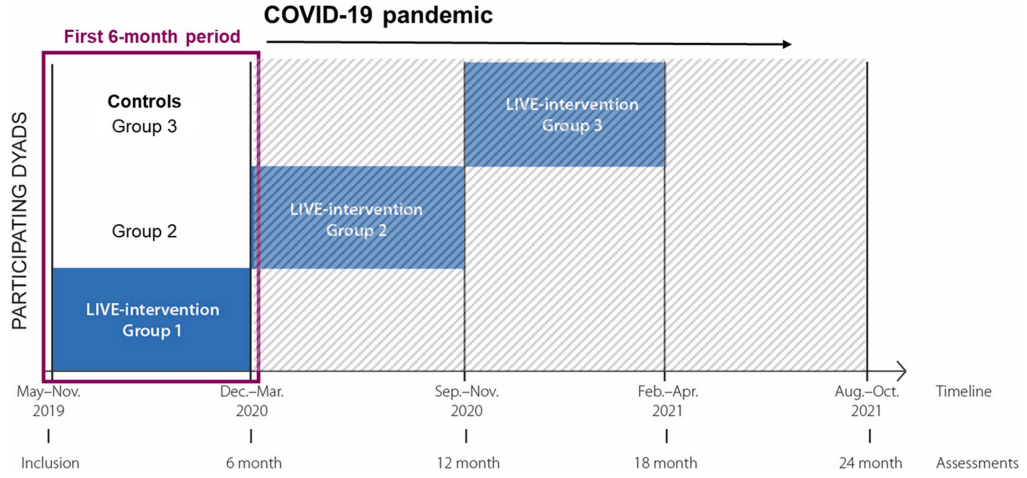


Fig. 1 The stepped-wedge closed-cohort randomized controlled LIVE@Home.Path trial during the COVID-19 pandemic. The COVID-19 pandemic temporarily halted the trial protocol at 6 months. This substudy includes all dyads (people with dementia and informal caregivers) who completed the first 6-month period, solely analyzing prepandemic data. In this first 6-month period, dyads randomized to Group 1 received the LIVE (*L*earning, *I*nnovation, *V*olunteer support, and *E*mpowerment) intervention while dyads randomized to Group 2 and Group 3 served as controls receiving health care as usual

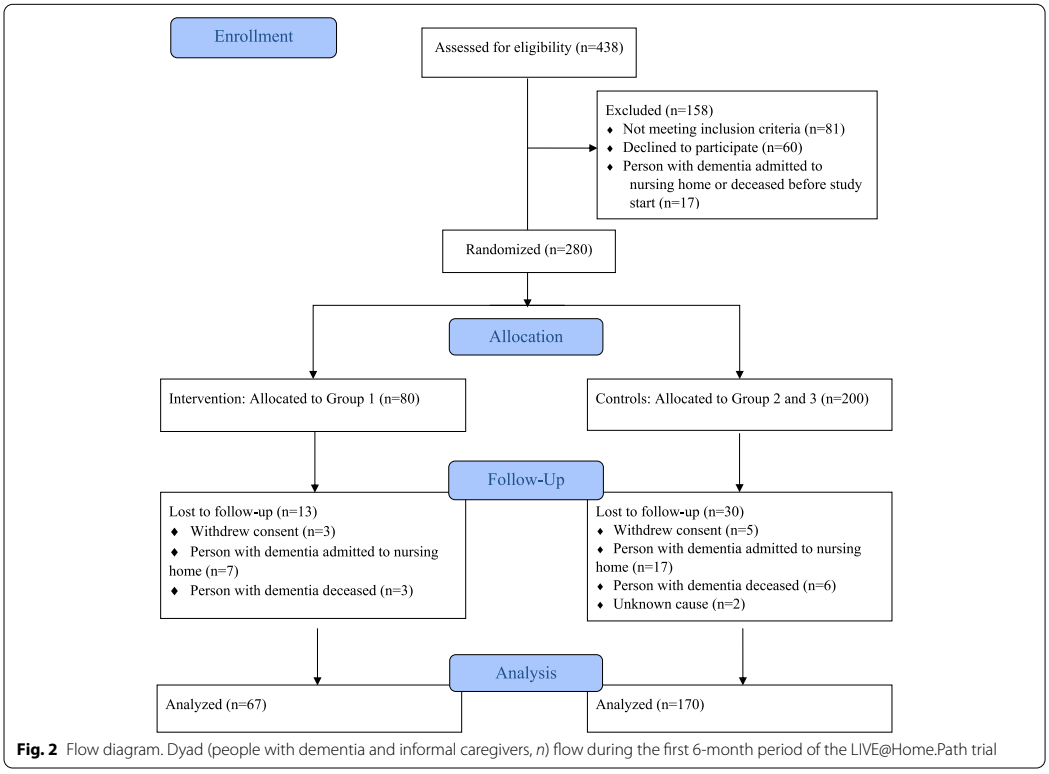


Fig. 2 Flow diagram. Dyad (people with dementia and informal caregivers, *n*) flow during the first 6-month period of the LIVE@Home.Path trial

Table 1 The multicomponent LIVE intervention implemented during the 6-month intervention period of the LIVE@Home.Path trial

	Learning	Innovation	Volunteer support	Empowerment
Content	Learning programs on dementia -Etiology, symptoms and disease course -Legal rights -Safety -Economy -Coping	Assess the need for, evaluate the usefulness of, and inform about relevant assistive technology and telecare -Passive sensors -Active sensors and tracking devices -Everyday technology -Video communication	Explore attitudes towards volunteer services and initiate contact with nonprofit organizations -The Red Cross -Norwegian Association of Public Health	Establish contact with the regular general practitioner to initiate: -Advanced Care Planning -Medication review
Participants	-PwD -Informal caregiver -Coordinator	-PwD -Informal caregiver -Coordinator	-PwD -Informal caregiver -Coordinator -Volunteers from nonprofit organizations matched by volunteer managers	-PwD -Informal caregiver -Coordinator -PwD's regular general practitioner

Each component of the intervention was implemented by a municipal coordinator

PwD people with dementia

intervention components, while we refer to the trial protocol for a full description that also covers the implementation process in detail [19]. The multicomponent intervention was developed using the theoretical framework by the UK Medical Research Council on complex interventions [15]. The intervention was designed to meet the requirements of the Dementia Plan 2020 by the Royal Norwegian Ministry of Health and Care Services, combining and adapting already existing evidence on how to support PwD [24, 25].

The coordinators were nurses, learning disability nurses, and occupational therapists experienced in dementia care already working in the home-based services of the designated municipalities. In the intervention period, each coordinator served approximately 5–7 dyads in addition to other municipal tasks not affiliated with the trial. The research group held two-day implementation seminars at the start of the intervention period to qualify the coordinators to adapt the intervention to the dyad's needs through lectures, role-plays, and discussions. Pocket manuals describing core features of the intervention guided coordinators in addressing all the intervention components. The coordinators used checklists to document to which extent they had introduced the dyads to the intervention components. To further standardize and secure implementation, we arranged one-day midway seminars halfway through the 6-month intervention period allowing for discussion of obstacles and pitfalls, and telephone follow-up for the coordinators every 14 days.

The coordinators paid the dyads at least two home visits and made monthly telephone calls during the 6-month intervention period. They provided the dyads with verbal and written information on the intervention components in the context of their municipality (Table 1) and established contact with the PwD's regular GP to inform on participation. If welcomed by the dyads, the coordinators requested a medication review directly from the PwD's regular GP using the electronic medical record and provided a report on BPSD, cognition, blood pressure, pulse, body mass index, pain, and caregiver burden (Relative Stress Scale) prior to the in-person consultation [19, 26]. The GPs evaluated the indication for medication reviews based on the report, medical history, and relevant laboratory tests. The informal caregivers and coordinators were encouraged to partake in the medication review in addition to the PwD to acquire a better understanding of the current symptoms and complaints, and to empower the PwD in discussing the use of medications and any wishes for treatment. The GPs were responsible for and made all final decisions regarding the PwD's medical treatment. Additional file 1 outlines the role of health care professionals involved in the conduction of LIVE@Home.Path trial.

Participants

We applied convenience sampling to recruit dyads from geriatric and gerontopsychiatric out-patient clinics, municipal memory teams, and general media with no financial incentives. Dyads were eligible if the PwD was ≥65 years, home-dwelling, and in face-to-face contact with the informal caregiver at least 1 h a week. Dementia, as diagnosed by the health care services, qualified individuals for participation regardless of etiology as long as their Mini-Mental Status Examination (MMSE) score was 15–26 or Functional Assessment Staging (FAST) score was 3–7 [19, 23, 27, 28]. A dyad was lost at follow-up if consents were withdrawn or if the PwD was permanently admitted to a nursing home or deceased.

Assessments and outcomes

The data collectors at municipal sites (nurses, learning disability nurses, occupational therapists) completed a one-day training program arranged by the research team to safeguard blinded and standardized data collection. Instructions were given both verbally and in writing. The researchers were available for answering any questions regarding the assessments and provided technical support, as well as assistance, during data collection. Data were immediately transferred to a secure server using tablets.

Primary outcomes

Changes in the numbers of prescribed psychotropic drugs, both in total and regular use, were calculated from baseline to month 6. The dyads reported all the prescription and over-the-counter medicines and supplements the PwD was currently using. The information was confirmed from prescriptions, drug packages, multi-dose drug dispensing, and/or medical records. All substances listed in the Anatomical Therapeutic Chemical Index (ATC) were classified as drugs [29]. The identity of the drugs was split, with those drugs set in a schedule regarded as "regular" and all others "on-demand." Psychotropic drugs were categorized according to ATC in antipsychotic (N05A), anxiolytic (N05B), hypnotic and sedative (N05C), antidepressant (N06A), and antidementia drugs (N06D).

Secondary outcomes

The Neuropsychiatric Inventory (NPI-12) was used to evaluate delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibitions, irritability, aberrant motor behavior, sleep disturbances, and appetite changes over the four preceding weeks at baseline and 6 months [30]. Multiplying frequency (1–4) and severity (1–3) generated a score for each of the twelve domains, with domain scores ≥4 indicating symptoms of clinical relevance [2]. Domain scores were added to yield the NPI-12 total score (0–144). According to a previous principal component analysis, subsyndrome scores for psychosis comprised delusions and hallucinations (0–24), hyperactive behavior included agitation, euphoria, irritation, disinhibition, and aberrant motor behavior (0–60), while depression, apathy, sleep disturbances, and appetite changes constituted the mood subsyndrome (0–48) [31].

The Cornell Scale for Depression in Dementia (CSDD) assessed the depressive symptoms of the past week at baseline and 6 months [32]. The nineteen items were rated "absent" (0), "mild or intermittent" (1) or "severe" (2), or "not possible to evaluate" (missing); these were then added to generate the CSDD total score (0–38). The CSDD total score ≥8 indicated depressive symptoms of clinical relevance [33]. NPI-12 and CSDD were selected due to robust psychometric properties [30, 32–34].

The Clinical Global Impression of Change (CGIC) [35] was adapted to measure meaningful change in communication with the PwD's regular GP as perceived by the informal caregivers. At six months, change compared to baseline was rated on a 11-point scale from − 5 "Very much worse" via 0 "No change" to 5 "Very much improved." A similar formulation has been applied in nursing homes [36].

Characteristics

At baseline, dementia etiology was classified following the International Classification of Diseases (ICD-10) [37], while MMSE (range: 0–30, a lower score indicates greater cognitive impairment) and FAST (range: 1–7, a higher score indicates lesser functioning) covered dementia severity [27, 28]. Dependency of daily living was assessed by Physical Self-Maintenance Scale (PSMS, range: 6–30) and Instrumental Activities of Daily Living Scale (IADL, range: 8–31), in which higher scores indicate higher dependency [38, 39]. Medical comorbidity was evaluated by the one-item General Medical Health Rating Scale (GMHR) as poor, fair, good, or excellent health [40]. Data on kinship, age, gender, and residency within the dyads were also registered. At 6 months, the dyads reported whether the GP had reviewed the PwD's medications in the preceding 6 months.

Statistical methods

The unequal variances *t*-test was used to compare the intervention to the control group by changes in 1.) psychotropic drug use and BPSD between time points and 2.) patient-GP communication. Pearson's chi-squared test was used to evaluate to what extent medication reviews were conducted (reach) as well as determine the attrition rates between groups. Subgroup analyses comparing 1.) characteristics across the intervention and control group, 2.) those who had their medications reviewed to those who did not within (a) the intervention and (b) control groups, and 3.) completers and non-completers were made at baseline using Pearson's chi-square test for categorical data, the unequal variances t-test for normally distributed data, and the Wilcoxon-Mann-Whitney test for non-normal data. Characteristics are presented by number (*n*) and percent; mean and standard deviation (SD); and median and interquartile range (IQR), respectively. Two-tailed *P* values <0.05 were regarded as significant. NPI-12 and CSDD total scores were generated without substitution when >80% of the instruments were answered by the informal caregivers. Otherwise, they were regarded as missing. For all data, missing ranged from 0 to 6% (CSDD total score at baseline). We performed all analyses with Stata/IC, release 17 (StataCorp LP, College Station, TX).

Results

Of the 438 dyads screened for participation in LIVE@Home.Path, 280 dyads were included from May to November 2019 (Fig. 2). Table 2 presents baseline characteristics for the 237 dyads still in study at 6 months, 67 of which received the intervention. Alzheimer's disease was the dementia etiology most frequently specified (*n*=86, 36%). Antidementia drugs were the most frequently used psychotropic drug class, being regularly prescribed to 112 (47%) PwD. Psychotropic drugs, apart from antidementia drugs, were regularly prescribed to 69 (29%) PwD, and 12 (5%) used two or more. The median NPI-12 total score was 12 (IQR 4 to 24), and 159 PwD (67%) displayed one domain or more of clinical relevance. Mood was the NPI-12 subsyndrome with the highest median score, namely 4.5 (IQR 0 to 11). The median CSDD total score was 5 (IQR 1 to 9*)*, and 73 (31%) of the overall sample suffered from depressive symptoms of clinical relevance.

During the 6-month intervention period, GPs reviewed the medications of 44 (66%) PwD in the intervention group and 72 (42%) of the controls (*P*=0.001) (Fig. 3). Within the intervention group, PwD who had their medications reviewed used psychotropic drugs more widely had higher levels of hallucinations and agitation and a lower level of functioning at baseline than their counterparts not receiving medication reviews (Additional file 2). In the control group, the GPs conducted medication reviews more often for women, those with greater cognitive impairments, and those using hypnotics/sedatives (data not shown).

From baseline to six months, changes in the use of psychotropic drugs and individual drug classes did not differ between the intervention and control groups using the unequal variances *t*-test (Table 3). Similarly, Table 3 shows that no differences in NPI-12 or CSDD were detected.

We found significant intervention effects regarding patient-GP communication (Table 3). The informal caregivers of PwD who had their medications reviewed reported improved patient-GP communication compared to those who did not have a medication review conducted. This was true for the intervention group (1.33 vs. 0.20, *P*=0.001) and control group (0.73 vs. 0.17,

Table 2 Baseline characteristics for people with dementia and informal caregivers in the LIVE@Home.Path trial

	Overall sample (*n*=237)		Intervention group (Group 1) (*n*=67)		Controls (Group 2 and 3) (*n*=170)		*P* value*
	n (%)	Mean (SD)/ median [IQR]	*n* (%)	Mean (SD)/ median [IQR]	*n* (%)	Mean (SD)/ median [IQR]	
Person with dementia							
Age		82 (7)		83 (7)		81 (7)	0.013*
Gender, female	149 (63)		46 (69)		103 (61)		0.268
Residency							0.657
Living alone	102 (43)		32 (48)		70 (41)		
Co-residing with the reporting caregiver	111 (47)		29 (43)		82 (48)		
Co-residing with someone else than the reporting caregiver	20 (8)		5 (7)		15 (9)		
Dementia etiology							0.207
Alzheimer's disease	86 (36)		22 (33)		64 (38)		
Vascular dementia	7 (3)		0 (0)		7 (4)		
Dementia in other diseases classified elsewhere	11 (5)		2 (3)		9 (5)		
Unspecified dementia	131 (55)		42 (63)		89 (52)		
MMSE		21 [18, 23]		21 [19, 24]		21 [17, 23]	0.295
FAST		4 [4, 4]		4 [4, 4.5]		4 [4, 4]	0.064
GMHR							0.026*
Poor health	5 (2)		0 (0)		5 (3)		
Fair health	74 (31)		30 (45)		44 (26)		
Good health	110 (48)		26 (39)		84 (49)		
Excellent health	40 (17)		9 (13)		31 (18)		
PSMS		10 [8, 12]		10 [8, 13]		10 [8, 11]	0.146
IADL		20 [15, 25]		20 [15, 25]		20 [15, 24]	0.566
Drugs in general							
Total number	221 (93)	5 [3, 7]	63 (94)	5 [4, 7]	158 (93)	5 [3, 7]	0.633#
Regularly	219 (92)	5 [3, 7]	62 (93)	5 [3, 7]	157 (92)	5 [3, 7]	0.810#
Psychotropic drugs							
Total number	159 (67)	1 [0, 1]	49 (73)	1 [1, 1]	110 (65)	1 [0, 1]	0.379#
Regularly	150 (63)	1 [0, 1]	44 (66)	1 [0, 1]	106 (62)	1 [0, 1]	0.870#
Antipsychotic drugs	11 (5)		4 (6)		7 (4)		
Anxiolytic drugs	5 (2)		2 (3)		3 (2)		
Hypnotic/sedative drugs	31 (13)		8 (12)		23 (14)		
Antidepressant drugs	31 (13)		8 (12)		23 (14)		
Antidementia drugs	112 (47)		32 (48)		80 (47)		
Regularly psychotropic drugs except for antidementia drugs	69 (29)	0 [0, 1]	20 (30)	0 [0, 1]	49 (29)	0 [0, 1]	0.970#
Concomitant use of psychotropic drugs except for antidementia drugs	12 (5)		2 (3)		10 (6)		
On-demand	17 (7)	0 [0, 1]	7 (10)	0 [0, 1]	10 (6)	0 [0, 1]	0.221#
Antipsychotic drugs	1 (0)		0 (0)		1 (1)		
Anxiolytic drugs	8 (3)		2 (3)		6 (4)		
Hypnotic/sedative drugs	9 (4)		6 (9)		3 (2)		
Antidepressant drugs	0 (0)		0 (0)		0 (0)		
Antidementia drugs	0 (0)		0 (0)		0 (0)		
NPI-12 total score		12 [4, 24]		15 [5, 26]		12 [3.5, 20]	0.166
NPI-12 subsyndromes							
Psychosis		0 [0, 2]		0 [0, 2]	0 [0, 2]		0.745
Hyperactive behavior		2 [0, 5]		2 [0, 8]	2 [0, 5]		0.579
Mood		6 [1, 12]		7 [1, 14]	4.5 [0, 11]		0.134

Table 2 (continued)

	Overall sample (*n*=237)		Intervention group (Group 1) (*n*=67)		Controls (Group 2 and 3) (*n*=170)		*P* value*
	n (%)	Mean (SD)/ median [IQR]	*n* (%)	Mean (SD)/ median [IQR]	*n* (%)	Mean (SD)/ median [IQR]	
NPI-12 domain scores							
Delusions	37 (16)	0 [0, 2]	8 (12)	0 [0, 1]	29 (17)	0 [0, 2]	0.631#
Hallucinations	16 (7)	0 [0, 0]	4 (6)	0 [0, 0]	12 (7)	0 [0, 0]	0.346#
Agitation	18 (8)	0 [0, 1]	4 (6)	0 [0, 1]	14 (8)	0 [0, 1]	0.530#
Depression	58 (24)	0 [0, 2]	20 (30)	1 [0, 6]	38 (22)	0 [0, 2]	0.169#
Anxiety	42 (18)	0 [0, 2]	16 (24)	0 [0, 2]	26 (15)	0 [0, 1]	0.451#
Euphoria	4 (2)	0 [0, 0]	0 (0)	0 [0, 0]	4 (2)	0 [0, 0]	0.718#
Apathy	65 (27)	0 [0, 4]	23 (34)	1 [0, 6]	42 (25)	0 [0, 4]	0.133#
Disinhibitions	19 (8)	0 [0, 1]	5 (7)	0 [0, 1]	14 (8)	0 [0, 1]	0.991#
Irritability	47 (20)	0 [0, 2]	16 (24)	0 [0, 3]	31 (18)	0 [0, 2]	0.574#
Aberrant motor behavior	28 (12)	0 [0, 0]	9 (13)	0 [0, 0]	19 (11)	0 [0, 0]	0.542#
Sleep disturbances	48 (20)	0 [0, 2]	12 (18)	0 [0, 1]	36 (21)	0 [0, 2]	0.745#
Appetite changes	65 (24)	0 [0, 3]	21 (31)	0 [0, 5]	44 (26)	0 [0, 3]	0.989#
≥ 1 NPI-12 domain of clinical relevance	159 (67)		49 (67)		110 (65)		0.252
CSDD total score	73 (31)	5 [1, 9]	22 (35)	6 [2, 9]	51 (30)	4.5 [1, 9]	0.573#
Informal caregiver							
Age		66 (12)		67 (13)		66 (12)	0.749
Gender, Female	152 (64)		44 (66)		108 (64)		0.816
Kinship to the person with dementia							0.765
Spouse	103 (43)		27 (40)		76 (45)		
Child	116 (49)		36 (54)		80 (47)		
Other	13 (5)		3 (4)		10 (6)		

n number of participants completing the first 6-month period, *SD* standard deviation, *IQR* interquartile range, *P* two-tailed *P* value, generated by Pearson's chi-square, unequal variances *t*-test, or Wilcoxon-Mann-Whitney test, regarded significant if <0.05 and marked *, #*P* value of comparison of non-normal or normal data when categorical data also is reported. *MMSE* Mini-Mental Status Examination, range 0–30, a lower score indicates greater impairment; *FAST* Functional Assessment Staging, range 1–7, a higher score indicates lesser functioning; *GMHR* General Medical Health Rating Scale; *PSMS* Physical Self-Maintenance Scale, range 6–30, a higher score indicates higher dependency; *IADL* Instrumental Activities of Daily Living Scale, range 8–31, higher score indicates higher dependency. Drugs were classified by the Anatomical Therapeutic Chemical Index; psychotropic drugs included antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, and antidementia drugs. *NPI-12* Neuropsychiatric Inventory, total score ranges 0–144, psychosis subsyndrome (delusions and hallucinations) ranges 0–24, hyperactive behavior (agitation, euphoria, irritation, disinhibition, aberrant motor behavior) ranges 0–60, mood (depression, apathy, sleep disturbances, and appetite changes) ranges 0–48, each domain ranges 0–12 with domain scores ≥4 indicating symptoms of clinical relevance; *CSDD* Cornell Scale for Depression in Dementia, total score ranges 0–38 and ≥8 indicate depressive symptoms of clinical relevance

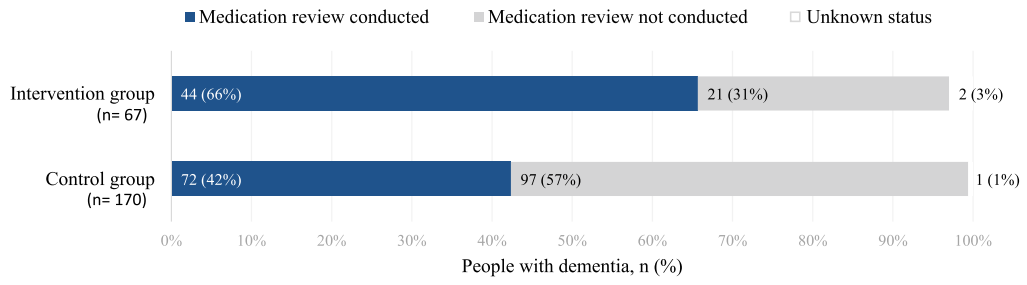


Fig. 3 Reach of medication reviews. Conduction of medication reviews for people with dementia (*n* (%)) during the first 6-month period of the LIVE@Home.Path trial

Table 3 Changes from baseline to 6 months for people with dementia in the LIVE@Home.Path trial

	Number of observations (overall sample)	Intervention group (Group 1) (*n*=67)		Controls (Group 2 and 3) (*n*=170)		*P* value*
	n	Mean	SD	Mean	SD	
Drugs in general						
Total number	213	0.32	2.17	0.29	1.94	0.944
Regularly	213	0.02	1.80	− 0.06	1.63	0.778
Psychotropic drugs						
Total number	213	0.02	0.81	0.06	0.62	0.718
Regularly	213	0.00	0.64	− 0.01	0.61	0.946
≥ 1 regularly	138	− 0.18	0.60	− 0.12	0.66	0.620
Classes regularly prescribed						
Antipsychotic drugs	213	− 0.02	0.13	0.00	0.00	0.321
Anxiolytic drugs	213	0.00	0.00	0.01	0.18	0.656
Hypnotic/sedative drugs	213	0.02	0.34	− 0.03	0.31	0.337
Antidepressant drugs	213	0.03	0.26	0.02	0.29	0.737
Antidementia drugs	213	− 0.03	0.45	0.00	0.43	0.623
Behavioral and psychological symptoms of dementia						
NPI-12 total score	220	2.57	18.60	2.64	16.60	0.982
NPI-12 subsyndromes						
Psychosis	237	0.54	3.73	0.79	4.23	0.647
Hyperactive behavior	237	2.66	7.96	1.34	7.98	0.252
Mood	237	− 0.46	11.15	0.51	9.23	0.527
NPI-12 domain scores						
Delusions	219	0.67	2.47	0.43	2.99	0.599
Hallucinations	219	0.03	2.27	0.35	2.29	0.353
Agitation	218	0.73	2.94	0.45	2.35	0.509
Depression	220	− 0.07	3.76	0.31	2.95	0.479
Anxiety	218	− 0.08	3.02	0.06	3.47	0.761
Euphoria	216	0.52	1.81	0.19	1.74	0.227
Apathy	218	0.03	4.47	0.30	4.01	0.685
Disinhibitions	216	0.32	2.68	− 0.17	2.28	0.219
Irritability	220	0.08	3.72	0.50	3.02	0.431
Aberrant motor behavior	218	1.13	3.57	0.14	3.08	0.059
Sleep disturbances	217	0.42	4.22	0.40	4.23	0.981
Appetite changes	219	− 1.23	4.62	0.35	3.59	0.183
CSDD total score	218	2.12	5.09	0.90	7.69	0.178
Patient-general practitioner communication by CGIC	230	0.95	1.68	0.41	1.34	0.022*

n number of participants completing the first 6-month period; *SD* standard deviation, *P* two-tailed *P* value, generated by unequal variance *t*-test, regarded significant if <0.05 and marked *. Drugs were classified by the Anatomical Therapeutic Chemical Index; psychotropic drugs included antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, and antidementia drugs. *NPI-12* Neuropsychiatric Inventory, total score ranges 0–144, psychosis subsyndrome (delusions and hallucinations) ranges 0–24, hyperactive behavior (agitation, euphoria, irritation, disinhibition, aberrant motor behavior) ranges 0–60, mood (depression, apathy, sleep disturbances, and appetite changes) ranges 0–48, each domain ranges 0–12. *CSDD* Cornell Scale for Depression in Dementia, total score ranges 0–38. Negative values indicate reductions in drugs and improvement on NPI and CSDD, while positive scores indicate drug increase and symptom deterioration. *CGIC* Clinical Global Impression of Change, range −5–5, negative scores indicate worsening, positive scores indicate improvement

P=0.011), as well as the overall sample (0.96 vs. 0.17, *P*<0.001) (Fig. 4).

The attrition rates from baseline to 6 months were similar in both groups: 16% in the intervention group and 15% in the control group (*P*=0.793). In most cases, dyads were lost at follow-up because the PwD was permanently admitted to a nursing home or deceased (Fig. 2). The non-completers (*n*=43) were older, had a lower level of functioning by FAST, a higher dependency in daily living activities by PSMS and IADL, and used antidementia drugs less often than the completers (*n*=237) (Additional file 3). We found the same differences when comparing

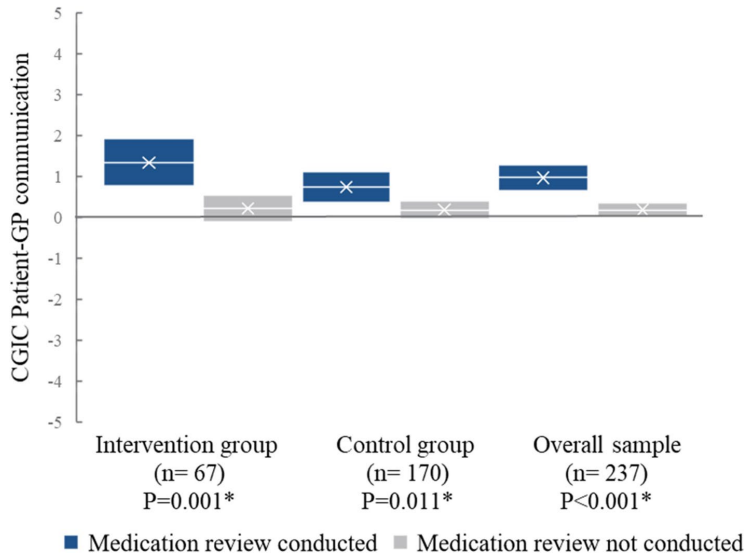


Fig. 4 Change in patient-general practitioner (GP) communication by medication reviews. Patient-GP communication as perceived by the informal caregivers stratified on whether medication reviews were conducted for people with dementia (*n*) during the first 6-month period of the LIVE@Home.Path trial. CGIC: Clinical Global Impression of Change, range −5–5, negative value: worsening, positive value: improvement. *P* values for difference in mean, marked * if <0.05, and 95% confidential interval by the unequal variances *t*-test

completers (n=237) to people lost at follow-up due to permanent nursing home care (n=24), the exceptions being higher NPI-12 total score (17.5, IQR 8 to 28.5, vs 12, IQR 4 to 24, P=0.036) and the number of NPI-12 domains of clinical relevance (2, IQR 1 to 3.5, vs 1, IQR 0 to 3, P=0.027).

Discussion

The multicomponent intervention of LIVE@Home.Path successfully increased the reach of medication reviews conducted by GPs, yet the process led to no change in psychotropic drug use or BPSD for home-dwelling PwD. Nevertheless, their informal caregivers perceived an improvement in communication with the GP. We argue that our control group serves as an example of an existing practice among Norwegian GPs for optimizing pharmacological BPSD management through medication reviews. Moreover, these established procedures can be even more cultivated, because our study shows that when GPs are encouraged, they increase the reach of revisions for home-dwelling PwD, leading to better communication.

This is the first study to evaluate the impact of GP conducted medication reviews on psychotropic drugs in home-dwelling PwD. Contrary to our primary hypothesis, we detected no impact on prescribing practices, although it was demonstrated that medication reviews reduce the number of psychotropic drugs prescribed in nursing homes [18, 41]. The pre-revision levels of psychotropic drugs used both regularly and on-demand were lower in our study than in the nursing home setting, which might make further reductions uncalled for. This is also illustrated by the German Delphi-MV trial enrolling persons living at home with mild cognitive impairment and dementia (n=407), in which interdisciplinary case conferences failed to reduce the number of potentially inappropriate drugs (24%) yet increased the use of antidementia drugs [42]. In a Finnish population-based sample of older adults (n=700), in which close to 40% used antipsychotics, benzodiazepines, and antidepressants, geriatricians outside the health care system were not able to reduce psychotropic drug use by structural medication assessments [43]. This reflects that deprescribing is challenging even for highly specialized physicians in populations with prevalent use. Nevertheless, the authors emphasized the potential of medication reviews in preventing psychotropic polypharmacy, above all in continuous patient-physician relationships allowing for careful considerations also before initiating new drugs [43]. In Norway, the cluster randomized controlled

COOP trial confirmed this view, concluding that even though regular GPs were less experienced than geriatricians in performing structured evaluations of complex pharmacotherapy, they contributed to collaborative medication reviews with valuable input as they knew their patients well [44]. A recent retrospective cohort study with a 1-year follow-up on 9324 patients with dementia in England concluded that higher continuity of GP care was associated with safer prescribing and lower rates of major adverse events [45]. Another retrospective study including 2250 new residents with dementia found that psychotropic drugs were dispensed at higher rates for those who changed GP when entering Australian residential care compared to those who continued seeing their regular GP [46]. This illustrates the importance of maintaining a continuous patient-GP relationship in preventing potentially inappropriate initiation of psychotropic medicines [45, 46]. The prescribing practices in our study likely reflect the considerable focus placed on limiting excessive psychotropic drugs among PwD in recent years, underscoring that the continuous deprescribing process is more than simply drug withdrawal [47].

Our data imply that the GPs conducted medication reviews based on their discretion concerning whether an evaluation would benefit the patient. Better interaction within primary care has been warranted for home-dwelling PwD, as an 18-month-long prospective study (n=599) showed that PwD consulted their GPs less often than other elderly persons receiving municipal health and social care services in Norway between 2009 and 2012 [48]. The national guideline for dementia strongly advises GPs to invite patients with dementia for routine checkups once or twice yearly to evaluate the need for medication reviews [6], and the GPs are reimbursed accordingly. We now demonstrate that GPs conduct medication reviews frequently (42%) and even more so when encouraged by the coordinators in LIVE@Home.Path (66%). This is in contrast to the 3.4% of consultations with patients over the age of 67 at GP level, coded as 'medication review' in the Norwegian Registry for Primary Health Care (NRPHC) of 2020 [49]. Of note, NRPHC does probably not catch all medication reviews in routine ambulatory GP care due to restrictions on use of reimbursement code combinations, nor contain complementary information on reasons, diagnoses, or outcomes. Additionally, the medication review reimbursement code accommodates specific formal requirements, unlike the reporting in our trial and direct comparisons can therefore not be made. Nonetheless, our findings align with a recent pragmatic prospective non-randomized intervention study confirming GPs' preparedness to conduct medication reviews, as three peer group meetings increased the frequency of revisions and improved prescription practice, both according to the GPs themselves and the process measures in NRPHC and the Norwegian Prescription Database [50]. In our trial, the electronic medical record infrastructure was crucial to enabling collaboration and engagement between PwD and formal and informal caregivers. Our findings are uplifting in that they show that GPs now readily optimize their patients' medications resulting in enhanced communication.

Even though we report BPSD levels close to what is reported at admission to nursing homes [12], earlier work shows that prescription rates of antidepressants, antipsychotics, anxiolytics, sedatives, and hypnotics persistently increase during the first 6 months stay [12, 46, 51]. In our study, the use of these medications was not associated with dropout due to nursing home admission, while on the contrary, impaired functioning, dependency in activities of daily living, and BPSD were associated with nursing home admission. The prospective DemVest study highlighted the pertinence of detecting and treating BPSD, as the 5-year course of these symptoms predicted functional deterioration independent of cognition in patients diagnosed with Alzheimer's disease and Lewy body dementia [4]. Further, benzodiazepines and Z-hypnotics exacerbated functional deterioration in this cohort of 196 patients, especially when combined with antidepressants [8]. In the multicomponent cluster randomized controlled COSMOS trial (n=428), we documented an improvement in activities of daily living in nursing home residents after careful withdrawal of psychotropic drugs, as decided by the physician in discussion with colleagues [17, 18]. Within the intervention group of our current study, the GPs prioritized their patients for revisions according to symptoms likely to compromise safety, higher numbers of psychotropic drugs prescribed, and lower level of functioning. Our interpretation is that the GPs acknowledge the need for revisions but that a limited facility to monitor clinical change makes them more conservative when adjusting prescriptions in the home-dwelling setting compared to institutions. Another point is that inherent prescribing procedures within the multidose dispensing system, which provides machine-dispensed tablets and capsules in disposable plastic bags to patients experiencing difficulties handling and administering drugs, may increase practical challenges with changing drug regimes. Further, the fragmented organizational structure of health care services may hamper collaboration between providers, health care professionals, and PwD and their informal caregivers. As our informal caregivers to home-dwelling PwD verified the experiences from nursing homes that medication reviews improved communication between

health personnel, patients, and their relatives [17], we advocate that it should be encouraged for PwD, regardless of the level of functioning and accommodation.

As this substudy concentrates on psychotropic prescribing practices, we considered medication reviews the most active ingredient within the intervention because the GPs can effectuate drug changes immediately. However, we acknowledge that it may be challenging to tease out the effects of single elements in multicomponent interventions and cannot exclude that the other components may exert more delayed effects on deprescribing [15, 16, 18, 22]. For example, increasing the dyads' knowledge of dementia management (i.e., the Learning component) could improve symptom awareness and strategies for non-pharmacological treatment of BPSD, thereby reducing the need for psychotropic drugs over time. However, we argue that with the regular GP scheme, the dyads are at higher readiness for medication reviews than for adopting the other and less familiar components of the intervention. Effective implementation in trials and real-world settings is highly dependent on contextual factors [15]. In the above example, the intention, initial decision, and commitment to attend the learning activity represent barriers [15, 52]. To evaluate implementation in our trial, we compared the reach of medication reviews across groups. Yet, applying measures of implementation outcomes could have aided us in answering questions around fidelity and quality of implementation, mechanisms of change, and context [15, 22, 52]. Notably, due to COVID-19, the process evaluation is not completed for the trial at the time of writing [19], as the final conference where we will inquire about the coordinators and other stakeholders' experiences is postponed. Nevertheless, a strong stakeholder incentive exists to promote the LIVE components in routine dementia care practice at present [24].

The primary strength of this study is that the participants completed assessments compiling validated, well-established and complementary instruments that were blindly and electronically administered by trained and supervised data collectors, securing data quality [19]. A considerable number of dyads were included from multiple sites and levels of health care services in Norway, thereby increasing the generalizability of our findings. The stepped-wedge design of LIVE@Home.Path was chosen in compliance with patient and public involvement, as it respects the randomization principle yet allows all participants to receive the intervention. This likely also led to low dropout rates due to withdrawal of consent.

We met COVID-19 related limitations in conducting this study. Due to the dramatically worsening care situation resulting in exacerbating BPSD and impinged trial protocol [23, 53, 54], we found it appropriate to solely analyze the prepandemic data from the first 6-month period despite compromising power and misbalancing group sizes (Fig. 1). Additionally, 19 dyads were assessed by phone rather than in person due to the outbreak, possibly lessening data quality regarding drugs and BPSD in these dyads.

This study additionally has non-COVID-19-related limitations. Firstly, our study sample was a convenience sample, and the non-random recruitment of dyads from health care services may limit the generalizability of our findings to people living with dementia somehow attended to and supported by formal and informal caregivers. Secondly, self-reports on medication may limit direct comparisons to other studies relying on data from medical records and registries. Our access was only sufficient to verify current drug consumption, and consequently, we did not inquire for prescriber details, indications, and duration of therapy. Thirdly, we did not explore the GPs' strategies for conducting medication reviews or evaluating drug therapy, or whether they involved other health care professionals. However, the risk that the GPs to PwD allocated to the control conditions altered their behavior (i.e., increase the frequency of revisions) when being studied is minuscule as they were not yet informed on participation. Fourthly, we did not provide the GPs with formalized collegial support, or integrations for decision support other than the reports and coordinators' involvement, and we cannot exclude the possibility that a more formalized and rigorous medication review would have yielded a greater reduction in psychotropic drug use. This pragmatic approach likely increases the variability, yet increases the external validity, of our study. Finally, the chance of false-positive findings in the subgroup analyses increases due to multiple testing.

Conclusions

Even though psychotropic drug use and BPSD were not affected by the multicomponent intervention, our study shows that patient-GP communication improved with medication review. Implementing medication reviews in routine care could achieve long-term benefits by increasing the continuity of care for this complex patient population. We advise GPs to conduct medication reviews regularly for patients with dementia, even when prescription and follow-up are within current standards; and suggest that they, if possible, should exercise collegial support in their local networks. We recommend that future studies explore medication reviews from the GP perspective to develop integrations for decision support in dementia care.

Abbreviations

ATC: Anatomical Therapeutic Index; BPSD: Behavioral and psychological symptoms of dementia; CGIC: Clinical Global Impression of Change; COVID-19:

Coronavirus SARS CoV-2 disease, 2019; CSDD: Cornell Scale for Depression in Dementia; FAST: Functional Assessment Staging; GMHR: General Medical Health Rating Scale; GP: General practitioner; IADL: Instrumental Activities of Daily Living; ICD-10: International Classification of Diseases, 10th version; LIVE: Learning; Innovation; Volunteer support; Empowerment; MMSE: Mini-Mental Status Examination; NPI-12 : Neuropsychiatric Inventory, 12-domain version; NRPHC: Norwegian Registry for Primary Health Care; PSMS: Physical Self-Maintenance Scale; PwD: People with dementia.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02382-5.

Additional file 1. The role of health care professionals involved in the conduction of the LIVE@Home.Path trial. Description: table.

Additional file 2. Baseline characteristics for people with dementia by medication review in the first intervention group of LIVE@Home.Path. Description: table.

Additional file 3. Baseline characteristics for people with dementia by attrition during the first 6-month period of LIVE@Home.Path. Description: table.

Acknowledgements

We thank Renira Angeles, Nathalie Puaschitz (postdoctoral fellows), and Eirin Hillestad (PhD candidate) for being cardinal in delivering seminars to the coordinators and assisting in data collection. The views of Rune Samdal (user representative) were always integrated. This entire research team thanks the dyads, coordinators, municipal staff and GPs in Bærum, Bergen, and Kristiansand for contributing to the trial. BSH are grateful to the G.C. Rieber Foundation and the Norwegian Government for supporting the work at the Centre for Elderly and Nursing Home Medicine, University of Bergen, Norway.

Authors' contributions

BSH was the primary investigator, having applied to the Research Council of Norway for trial funding and recruited the participating municipalities. BSH, MHG, MV, and LIB arranged and delivered all seminars essential to conducting the trial. JM randomized the dyads. MHG and MV trained and supported the data collectors and contributed to data collection together with LIB. BSH, MHG, JM, MN, and LIB planned this study. MHG analyzed and presented the data with supervision from JM, who verified the statistical procedures and interpretation. MHG and LIB wrote the first draft in collaboration. All authors (MHG, BSH, JM, MN, GS, MV, and LIB) read, critically reviewed, and approved the final manuscript.

Funding

The Research Council of Norway (273581) and the Dignity Centre funded the trial. The Research Council of Norway (273581) sponsored the positions of MHG, JM, MV, and LIB. The Centre for Elderly and Nursing Home medicine at the University of Bergen, which was responsible for conducting the trial, is funded by GC Rieber Foundations and the Norwegian Government. The funders had no role in planning the design of the study, nor in the collection, management, analysis, and interpretation of data. They had no part in writing of the manuscript and no influence on the decision to choose a journal for publication.

Availability of data and materials

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

Declarations

Ethics approval and consent to participate

Each participant in the dyads provided spoken and written consent for participation after verbal and written information. If the PwD were not regarded capable, the informal caregiver or a legal advocate provided consent based on his/her determination of whether the person would have agreed to participate if he/she had the ability. Before we recruited participants, the Regional Committee for Medical and Health Research Ethics North Norway (2019/385) and the Norwegian Centre for Research Data (514093) approved the trial, and ClinicalTrials.gov indexed (NCT04043364) it. In addition, the University of Bergen archived the Data Protective Impact Assessment (ePhorte 2019/5569).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Centre for Elderly and Nursing Home Medicine, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway. [2]Haraldsplass Deaconess Hospital, Bergen, Norway. [3]Municipality of Bergen, Bergen, Norway. [4]Section for Epidemiology and Medical Statistic, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway. [5]Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway. [6]Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway. [7]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. [8]Geriatric Department, Oslo University Hospital, Oslo, Norway. [9]NKS Olaviken Gerontopsychiatric Hospital, Askøy, Norway.

Received: 26 January 2022 Accepted: 25 April 2022
Published online: 26 May 2022

References

1. World Health Organization. Dementia fact sheet. World Health Organization. 2021. https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed 18 Jan 2022.
2. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. Br J Psychiatry. 2020;216:43–8.
3. Wergeland JN, Selbaek G, Bergh S, Soederhamn U, Kirkevold Ø. Predictors for Nursing Home Admission and Death among Community-Dwelling People 70 Years and Older Who Receive Domiciliary Care. Dement Geriatr Cogn Disord. 2015;5:320–9.
4. Borda MG, Aarsland D, Tovar-Rios DA, Giil LM, Ballard C, Gonzalez MC, et al. Neuropsychiatric Symptoms and Functional Decline in Alzheimer's Disease and Lewy Body Dementia. J Am Geriatr Soc. 2020;68:2257–63.
5. Bessey LJ, Walaszek A. Management of Behavioral and Psychological Symptoms of Dementia. Curr Psychiatry Rep. 2019;21:66.
6. Helsedirektoratet. Nasjonal faglig retningslinje for demens [National professional guidelines on dementia]. Helsedirektoratet. 2017; https://www.helsedirektoratet.no/retningslinjer/demens. Accessed 8 Mar 2020.
7. Watt JA, Goodarzi Z, Veroniki AA, Nincic V, Khan PA, Ghassemi M, et al. Safety of pharmacologic interventions for neuropsychiatric symptoms in dementia: a systematic review and network meta-analysis. BMC Geriatr. 2020;20:212.
8. Borda MG, Jaramillo-Jimenez A, Oesterhus R, Santacruz JM, Tovar-Rios DA, Soennesyn H, et al. Benzodiazepines and antidepressants: Effects on cognitive and functional decline in Alzheimer's disease and Lewy body dementia. Int J Geriatr Psychiatry. 2021;36:917–25.
9. Richardson K, Loke YK, Fox C, Maidment I, Howard R, Steel N, et al. Adverse effects of Z-drugs for sleep disturbance in people living with dementia: a population-based cohort study. BMC Med. 2020;18:351.
10. Bargagli AM, Cascini S, Agabiti N, Kirchmayer U, Marino C, Davoli M. Determinants Of Antipsychotic Drugs Prescription Among Community-Living Older Adults With Dementia: A Population-Based Study Using Health Information Systems In The Lazio Region. Italy. Clin Interv Aging. 2019;14:2071–83.
11. Sundseth AC, Gjelstad S, Straand J, Rosvold EO. General practitioners' prescriptions of benzodiazepines, Z-hypnotics and opioid analgesics for elderly patients during direct and indirect contacts. A cross-sectional, observational study. Scand J Prim Health Care. 2018;36:115–22.
12. Callegari E, Benth JŠ, Selbæk G, Lic CG, Bergh S. Does Psychotropic Drug Prescription Change in Nursing Home Patients the First 6 Months After Admission? J Am Med Dir Assoc. 2021;22:101–8.

13. Strand BH, Vollrath MEMT, Skirbekk VF. Dementia. In: Public Health Report - Health Status in Norway. The Norwegian Institute of Public Health; 2018. https://www.fhi.no/en/op/hin/health-disease/dementia-in-norway.
14. Sawan MJ, Moga DC, Ma JM, Ng JC, Johnell K, Gnjidic D. The value of deprescribing in older adults with dementia: a narrative review. Expert Rev Clin Pharmacol. 2021;14:1367–82.
15. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: an update of Medical Research Council guideance. BMJ. 2021;374:n2061.
16. Ballard C, Orrell M, YongZhong S, Moniz-Cook E, Stafford J, Whittaker R. Impact of antipsychotic review and nonpharmacological intervention on antipsychotic use, neuropsychiatric symptoms, and mortality in people with dementia living in nursing homes: a factorial cluster-randomized controlled trial by the well-being and health for people with dementia (WHELD) program. Am J Psychiatry. 2016;173:3.
17. Gulla C, Flo E, Kjome RLS, Husebo BS. Implementing a novel strategy for interprofessional medication review using collegial mentoring and systematic clinical evaluation in nursing homes (COSMOS). BMC Geriatr. 2019;19:130.
18. Gedde MH, Husebo BS, Mannseth J, Kjome RLS, Naik M, Berge LI. Less is more: The Impact of Deprescribing Psychotropic Drugs on Behavioral and Psychological Symptoms and Daily Functioning in Nursing Home Patients. Results from the Cluster-Randomized Controlled COSMOS Trial. Am J Geriatr Psychiatry. 2020;29:304–15.
19. Husebo BS, Allore H, Achterberg W, Angeles R, Ballard BF, et al. LIVE@ Home.Path—innovating the clinical pathway for home-dwelling people with dementia and their caregivers: study protocol for a mixed-method, stepped-wedge, randomized controlled trial. Trials. 2020;21:510.
20. Wimo A, Gustavsson A, Jönsson L, et al. Application of Resource Utilization in Dementia (RUD) instrument in a global setting. Alzheimers Dement. 2013;9:429–35.
21. Schulz R, et al. End-of-life care and the effects of bereavement on family caregivers of persons with dementia. N Engl J Med. 2003;349:1936–42.
22. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614.
23. Gedde MH, Husebo BS, Erdal A, Paschitz N, Vislapuu M, Angeles RC, et al. Access to and interest in assistive technology for home-dwelling people with dementia during the COVID-19 pandemic (PAN.DEM). Int Rev Psychiatry. 2020;33:404–11.
24. Ministry of Health and Care Services. The Dementia Plan 2020. Oslo (Norway): The Ministry of Health and Care Services; 2015.
25. Fæø SE, Tranvåg O, Samdal R, Husebo BS, Bruvik FK. The compound role of a coordinator for home-dwelling persons with dementia and their informal caregivers: qualitative study. BMC Health Serv Res. 2020;20:1045.
26. Ulstein I, Wyller TB, Engedal K. The relative stress scale, a useful instrument to identify various aspects of carer burden in dementia? Int J Geriatr Psychiatry. 2007;22:61–7.
27. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State - Practical Method for Grading Cognitive State of Patients for Clinician. J Psychiatr Res. 1975;12:189–98.
28. Reisberg B. Functional assessment staging (FAST). Psychopharmacol Bull. 1988;24:653–9.
29. ATC/DDD Index. WHO collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health, Oslo. 2015. https://www.whocc.no/atc_ddd_index/. Accessed 01 June 2019.
30. Cummings J. The Neuropsychiatric Inventory: Development and Applications. J Geriatr Psychiatry Neurol. 2020;33:73–84.
31. Aalten P, de Vugt ME, Lousberg R, Korten E, Jaspers N, Senden B, et al. Behavioral Problems in Dementia: A Factor Analysis of the Neuropsychiatric Inventory. Dement Geriatr Cogn Disord. 2003;15:99–105.
32. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biol Psychiatry. 1988;23:271–84.
33. Barca ML, Engedal K, Selbæk G. A Reliability and Validity Study of the Cornell Scale among Elderly Inpatients, Using Various Clinical Criteria. Dement Geriatr Cogn Disord. 2010;29:438–47.
34. 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;20:1–9.
35. Guy W. ECDEU assessment manual for psychopharmacology. Rockville: US Department of Health, Education and Welfare; 1976.
36. Aasmul I, Husebo BS, Sampson EL, Flo E. Advance Care Planning in Nursing Homes – Improving the Communication Among Patient, Family, and Staff: Results From a Cluster Randomized Controlled Trial (COSMOS). Front. Psychol. 2018;9:2284.
37. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
38. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179–86.
39. Lawton MP. Aging and performance of home tasks. Hum Factors. 1990;32:527–36.
40. Lyketsos CG, Galik E, Steele C, Steinberg M, Rosenblatt A, Warren A, et al. The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia. J Am Geriatr Soc 1999;47:487-491.
41. Mesquida MM, Casas MT, Sisó AF, Muñoz IG, Vian ÓH, Monserrat PT. Consensus and evidence-based medication review to optimize and potentially reduce psychotropic drug prescription in institutionalized dementia patients. BMC Geriatr. 2019;19:7.
42. Thyrian JR, Hertel J, Wucherer D, Eichler T, Michalowsky B, Dreier-Wolfgramm A, et al. Effectiveness and Safety of Dementia Care Management in Primary Care: A Randomized Clinical Trial. JAMA Psychiatry. 2017;74:996–1004.
43. Rikala M, Korhonen MJ, Sulkava R, Hartikainen S. The effects of medication assessment on psychotropic drug use in the community-dwelling elderly. Int Psychogeriatr. 2011;23:473–84.
44. Romskaug R, Skovlund E, Straand J, Molden E, Kersten H, Pitkala KH, et al. Effect of Clinical Geriatric Assessments and Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Home-Dwelling Older Patients Receiving Polypharmacy: A Cluster Randomized Clinical Trial. JAMA Intern Med. 2019;180:181–9.
45. Delgado J, Evans PH, Gray DP, Sidaway-Lee K, Allan L, et al. Continuity of GP care for patients with dementia: impact on prescribing and the health of patients. Br J Gen Pract. 2022. https://doi.org/10.3399/BJGP.2021.0413.
46. Welberry HJ, Jorm LR, Schaffer AL, Barbieri S, Hsu B, Harris MF, et al. Psychotropic medicine prescribing and polypharmacy for people with dementia entering residential aged care: the influence of changing general practitioners. Med J Aust. 2021;215:130–6.
47. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing'with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80:1254–68.
48. Ydstebø A, Bergh S, Selbæk G, Benth JŠ, Lurås H, Vossius C. The impact of dementia on the use of general practitioners among the elderly in Norway. Scand J Prim Health Care. 2015;33:199–205.
49. Legemiddelgjennomgang utført av fastleger [Medication reviews conducted by general practitioners]. Helsedirektoratet, Oslo. 2021. https://www.helsedirektoratet.no/statistikk/statistikk-om-allmennlegetjenester/legemiddelgjennomgang-utfort-av-fastleger. Accessed 14 Apr 2021.
50. Øyane NMF, Finckenhagen M, Ruths S, Thue G, Lindahl AK. Improving drug prescription in general practice using a novel quality improvement model. Scand J Prim Health Care. 2021;39:174–83.
51. O'Connor DW, Griffith J, McSweeney K. Changes to psychotropic medications in the six months after admission to nursing homes in Melbourne Australia. Int. Psychogeriatr. 2010;22:1149–53.
52. Mettert K, Lewis C, Dorsey V, Halko H, Weiner B. Measuring implementation outcomes: An updated systematic review of measures psychometric properties. Implementation Res. and Prac. 2020;1:1–29.
53. Vislapuu M, Angeles RC, Berge LI, Kjerstad E, Gedde MH, Husebo B. The consequences of COVID-19 lockdown for formal and informal resource utilization among home-dwelling people with dementia: results from the prospective PAN.DEM study. BMC Health Serv Res. 2021;21:1003.
54. Gedde MH, Husebo BS, Vahia IV, Mannseth J, Vislapuu M, Naik M, et al. The impact of COVID-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: a prospective cohort study (PAN.DEM). BMJ Open. 2022;12:e050628.

Publisher's Note

Paper III

Gedde MH, Husebo B, Vahia IV, Mannseth J, Vislapuu M, Naik M, Berge LI: The impact of Covid-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: a prospective cohort study (PAN.DEM). BMJ Open 2022;12:e050628.

BMJ Open

Impact of COVID-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: a prospective cohort study (PAN.DEM)

Marie H Gedde ,[1,2] Bettina S Husebo,[2,3] Ipsit V Vahia,[4,5] Janne Mannseth,[6] Maarja Vislapuu,[2] Mala Naik,[1,7] Line I Berge[2,8]

To cite: Gedde MH, Husebo BS, Vahia IV, *et al*. Impact of COVID-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: a prospective cohort study (PAN.DEM). *BMJ Open* 2022;**12**:e050628. doi:10.1136/bmjopen-2021-050628

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-050628).

Received 25 February 2021
Accepted 05 January 2022

For numbered affiliations see end of article.

Correspondence to
Dr Marie H Gedde;
marie.gedde@uib.no

ABSTRACT

Objectives To investigate the impact of the COVID-19 restrictions on behavioural and psychological symptoms of dementia (BPSD).

Design Prospective cohort study (PAN.DEM) nested within the halted parent trial (LIVE@Home.Path).

Setting Households in Norway immediate before and 6–9 weeks into the COVID-19 restrictions.

Participants 104 dyads (persons with mild to moderate dementia aged ≥65 and their informal carers) completed both prepandemic and pandemic assessments, among 237 in the parent trial. Mini-Mental Status Examination score 15–26 or Functional Assessment Staging score 3–7 covered dementia severity.

Main outcome measures Neuropsychiatric Inventory (NPI-12) total (range 0–144), psychosis (range 0–24), hyperactive behaviour (range 0–60) and mood subsyndrome (range 0–48) scores; Cornell Scale for Depression in Dementia (CSDD) total score (range 0–38).

Results We found an overall increase in BPSD by NPI-12 total score comparing prepandemic to pandemic levels (median 16 IQR (4.5–29) to 20 (7–32.5), p=0.03) over a mean of 86 days (SD 19). NPI-12 total score worsened in 57 (55%) of people with dementia and was associated with postponed or averted contacts with healthcare professionals (logistic regression, OR 3.96, 95% CI 1.05 to 14.95). Psychosis subsyndrome levels increased (0 (0–3) to 0.5 (0–6), p=0.01) in 37 (36%) persons; this worsening was associated with partial insight (9.57, 1.14 to 80.71) and reduced informal carer contact (4.45, 1.01 to 19.71). Moreover, depressive symptoms increased as assessed by CSDD total score (5 (3–9) to 7 (4–12), p=0.01) and worsened for 56 (54%), which was inversely associated with psychotropic drugs on-demand (0.16, 0.03 to 0.75).

Conclusions BPSD worsened during the first months of the COVID-19 restrictions, most pronounced for psychosis and depression. These BPSD exacerbations have implications for pandemic policies, emphasising that restrictions must balance COVID-19 morbidity and mortality against dementia deterioration.

Trial registration number NCT04043364; Results.

Strengths and limitations of this study

- ► This is the first prospective cohort study investigating the impact of the COVID-19 restrictions on behavioural and psychological symptoms of dementia (BPSD).
- ► The same informal carers reported BPSD for each home-dwelling person with dementia both before and during the pandemic scenario using validated, well-established instruments.
- ► The COVID-19 restrictions left some informal carers with less basis of observation, as 28% reported reduced contact with the person with dementia.
- ► Our study captures the impact of the initial phase of the outbreak in Norway and does not describe the long-term impact of the COVID-19 restrictions on BPSD.

INTRODUCTION

Dementia is among the most critical risk factors for COVID-19 mortality.[1] In England and Wales alone, 12 869 people with dementia have died, accounting for 26% of the COVID-19 death toll.[2] Until vaccination is widely available globally, hygiene and physical distancing interventions will remain cornerstones of protecting vulnerable populations.[3] The subsequent restrictions have been disrupting for home-dwelling people with dementia as private homes were not accessible to family members and volunteers, day care centres closed and home nursing services were restricted to those most in need. As a result, people with dementia living in the community are not only at risk from COVID-19 morbidity and mortality; they are also threatened from unforeseen effects of the restrictions.[4 5]

Behavioural and psychological symptoms of dementia (BPSD) cover a wide range of

clinical presentation including depression, anxiety, agitation and psychosis. Longitudinally, persistent BPSD may be found in up to 80% of people with dementia.[6] BPSD are best managed with structured, non-pharmacological interventions, placing psychotropic drugs as secondary treatment options.[7] Preliminary evidence indicates that BPSD may be exacerbated under the COVID-19 restrictions. Eight weeks into the Argentinian quarantine, informal carers reported worsening of anxiety, insomnia and depression among persons at different stages of Alzheimer's and related dementias living at home (N=119).[8] In another study, family carers stated worsening BPSD in 60% of Italian outpatients with various stages and aetiologies of dementia 1 month into the pandemic (N=4913).[9] This study also found that 28% required changes in psychotropic medication to address irritability, apathy, agitation and depression. Further, nursing home patients separated from the outside world in France with mild Alzheimer's disease reported increased anxiety and depression when asked to evaluate their own experience of the pandemic retrospectively (N=58).[10]

However, all these studies are cross-sectional and thus far, there is a dearth of longitudinal data tracking changes in BPSD during COVID-19 by comparing prepandemic to pandemic rates.[11] In this study, we aim to address this significant gap in the literature using data from the prospective PAN.DEM study.[12] This study is nested within the ongoing LIVE@Home.Path trial[13] and was launched by our team to investigate the impact of the COVID-19 restrictions (implemented in Norway on 12 March 2020) on home-dwelling people with dementia. Here, we present comparisons of prepandemic and pandemic BPSD, and explore factors associated with worsening BPSD.

METHODS

Study design

This is a prospective cohort study comparing the prepandemic assessment of BPSD of the parent trial, LIVE@Home.Path, to the PAN.DEM assessment.

Setting

The parent trial is a stepped-wedge randomised controlled trial.[13] It compares the cost-effectiveness in resource utilisation of a 6-month multicomponent intervention comprising Learning, Innovation, Volunteers and Empowerment to usual conditions for dyads of home-dwelling people with dementia and their informal carers. Trained data collectors blindly assessed all dyads in direct conversation every 6 months for 2 years (2019–2021). The prepandemic 6-month assessment was close to complete when the COVID-19 restrictions replaced trial protocol (figure 1A). Physical distancing (ie, restrictions on gatherings, public transport closure, stay at home-regulations and limitations on movement) formed the basis for the restrictions,[3] which implied that healthcare was limited to those most in need.[12] In response, we developed the semistructured PANdemic in DEMentia (PAN.DEM) telephone interview for informal carers to capture if, and how, dyads were affected by the outbreak (online supplemental file). This assessment included selected instruments from the parent trial in addition to questions regarding the pandemic. We consecutively invited as many dyads as possible from the parent trial to complete the PAN.DEM assessment from week 6 of restrictions until eased the 9th week (20 April 2020 to 15 May 2020). Potential respondents were considered unreachable when no response was given to two calls and a text message.

Participants

Dyads were eligible for inclusion in the parent trial if the persons with dementia were: ≥65 years, diagnosed with dementia (with Mini-Mental Status Examination (MMSE) score 15–26 or Functional Assessment Staging (FAST) score 3–7)[14 15]; home-dwelling in one of three Norwegian municipalities; and had weekly face-to-face contact with the informal carer. Dyads gave informed spoken and written consent for participation in the parent trial as described in the protocol.[13] Informal carers gave additional informed consent to PAN.DEM.[12]

Measurements

The primary outcome was change in BPSD between the prepandemic and pandemic assessments. We administered two informal carer-rated scales at both time points: (1) The Neuropsychiatric Inventory (NPI-12) assesses frequency and severity of delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibitions, irritability, aberrant motorial behaviour, sleep disturbances and appetite changes over the four preceding weeks.[16] Each of these 12 domains is scored from 0 (no symptoms) to 12 (very severe symptoms), a score ≥4 is regarded a BPSD with symptom load of clinical relevance.[6] These domains are further aggregated to generate subsyndrome scores for psychosis comprised of delusions and hallucinations (0–24), hyperactive behaviour comprised agitation, euphoria, irritation, disinhibition, aberrant motor behaviour (0–60), mood comprised depression, apathy, sleep disturbances and appetite changes (0–48), and finally, a total NPI-12 score (0–144);[17] (2) The Cornell Scale for Depression in Dementia (CSDD) assesses nineteen items of depressive symptoms during the prior week, each rated from 'absent' to 'severe' (0–2) or 'symptoms not possible to evaluate' (missing).[18] Adding item scores generate the CSDD total score (0–38).[18] A CSDD total score ≥8 indicates depression of clinical relevance.[19] The Norwegian versions of NPI-12 and CSDD have robust psychometric properties.[16 18–20]

In addition to BPSD, we collected the following data at the prepandemic assessment: the persons with dementia's level of functioning in activities of daily living by Physical Self-Maintenance Scale (PSMS)[21] and Instrumental Activities of Daily Living Scale (IADL),[22] health by the General Medical Health Rating Scale (GMHR),[23] possible dementia aetiology following the International Classification of Diseases-10th version,[24] and use of

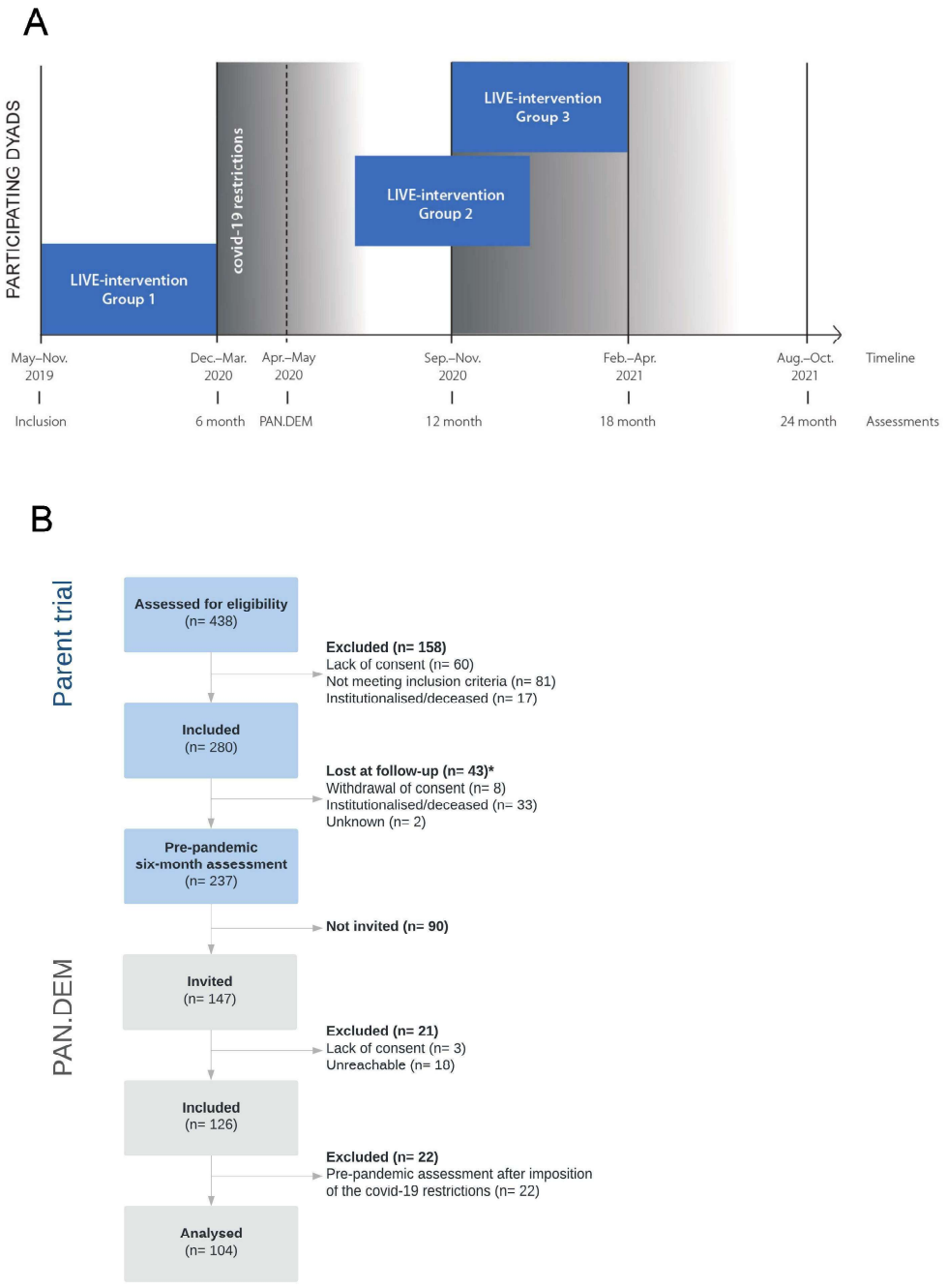


Figure 1 The parent trial, LIVE@Home.Path, including PAN.DEM. The COVID-19 restrictions replaced trial protocol from 12 March to eased on 15 May 2020. None of the dyads (person with dementia and informal carer, n) received the intervention while the PAN.DEM interviews were conducted (20 April 2020 to 15 May 2020). (A) Timeline. Vertical lines indicate assessments. The shaded parts illustrate the COVID-19 restrictions, postponing the Learning, Innovation, Volunteers and Empowerment (LIVE-Intervention) for the dyads of group 2. (B) Flow chart. This study includes the dyads of PAN.DEM completing the prepandemic assessment before the COVID-19 restrictions was implemented on 12 March 2020. *Parent trial attrition: rate within assumptions of lost to follow-up.

healthcare services and medications as specified by the dyads. Drugs catalogued in the Anatomical Therapeutic Chemical Index (ATC) administered in a set schedule were regarded 'regular', whereas all others were documented as 'on demand'.[25] Psychotropic drugs included antipsychotic (N05A), anxiolytic (N05B), hypnotic and sedative (N05C), antidepressant (N06A) and antiementia drugs (N06D) by ATC. Demographical data (age, gender, residency, kinship) were self-reported. We evaluated dementia severity in terms of cognition with MMSE and level of functioning with FAST at inclusion.[14 15]

At the pandemic assessment, the informal carers were also asked to estimate the degree of insight presented by the person with dementia into the COVID-19 situation and change in (1) contact with the informal carer, (2) volunteering services and (3) municipal healthcare services (home nursing services, home help, day-care, and in-home and out-of-home respite care) due to the COVID-19 restrictions.[12] Finally, informal carers stated if contacts with healthcare professionals were postponed or averted.

Study size

This study includes all dyads in PAN.DEM completing the prepandemic assessment before the COVID-19 restrictions were effectuated (figure 1B).

Statistical methods

Initially, we aggregated median and IQR, and calculated NPI-12 subsyndrome scores and total scores for NPI-12 and CSDD if >80% of the scales were answered. We used the Wilcoxon matched-pairs signed-rank test to assess change between the prepandemic and pandemic assessments. Next, we dichotomised those NPI-12 and CSDD sum scores that changed into worsening/not worsening and used multiple logistic regression analysis to explore factors associated. We included the following covariates for persons with dementia: age, gender, residency, dementia aetiology, MMSE, FAST, IADL, PSMS, GMHR, number of psychotropic drugs prescribed regularly and on-demand, and the COVID-19 specific outcomes. We also included age and gender of the informal carers. Covariates were selected based on our expertise in research and clinical dementia care. The Akaike information criterion guided model selection. Selected models were then checked for multicollinearity, robustness and goodness-of-fit by Pearson and Hosmer-Lemeshow test. FAST, IADL and PSMS showed moderate to strong positive correlation, but including all three covariates substantially improved the models. Missing data were handled with listwise deletion, with 14% missing any covariates. Calculations are expressed in OR with 95% CI, and p value. Reported p values are two tailed, and p<0.05 was considered statistically significant. Descriptive statistics are presented by n (%), mean (SD), or median (IQR). We used Stata/IC, release V.16 (StataCorp) for all analyses.

Public and Patient involvement

The conceptualisation, design, assessments and conduct of the parent trial as well as PAN.DEM included close patient/informal carer and public involvement.[12 13] A user-representative participated in the research group's weekly meetings. In PAN.DEM, he consulted with the study team on priorities, length and wording of the interview, and its revisions, with a special focus on the potential burden on informal carers.[12]

RESULTS

Of the 280 dyads participating in the parent trial, 237 completed the prepandemic assessment from December 2019 to March 2020 (figure 1B). This study includes 104 dyads recruited to PAN.DEM completing the prepandemic assessment before the COVID-19 restrictions were effectuated 12 March 2020. Mean time between assessments was 86 days (SD 19).

Table 1 shows that the mean age for people with dementia was 82 years (SD 7), 61% were women, 44% lived alone, and 50% received daily home-nursing services prior to the COVID-19 restrictions. Alzheimer's disease constituted the most common dementia aetiology, while 6% had vascular dementia and 10% reported Lewy-body dementia or Parkinson's disease. Most people with dementia lacked insight into the COVID-19 situation (table 2). The informal carers reported to have less contact with the person with dementia in 28% under the restrictions, and that contacts with healthcare professionals had been postponed or averted in 31%.

From the prepandemic to the pandemic assessment, people with dementia experienced an increase in NPI-12 total score (16 (4.5–29) to 20 (7–32.5), p=0.03) and in numbers of BPSD with symptom load of clinical relevance (2 (0–4) to 3 (1 –5), p<0.001) (table 3). Also, the NPI-12 score worsened for 55% (figure 2). We found an increase in the psychosis subsyndrome (0 (0–3) to 0.5 (0–6), p=0.01), with 36% experiencing more severe symptoms (figure 2). We also found an increase in depressive symptoms measured both by the NPI-12 depression domain (0 (0–3) to 1 (0–6), p=0.04) and CSDD total score (5 (3–9) to 7 (4–12), p=0.01, table 3). Additionally, the CSDD total score worsened for 54% (figure 2).

Table 4 shows the results of the logistic regression models exploring factors associated with worsening BPSD under the restrictions. Worsening NPI-12 total score was associated with postponed or averted contacts with healthcare professionals (OR 3.96, 95% CI 1.05 to 14.95) and impaired cognition as indicated by MMSE (OR 1.19, 95% CI 1.01 to 1.40), while a diagnosis of Alzheimer's disease relative to other dementia aetiologies was associated with lower OR of worsening NPI-12 (OR 0.18, 95% CI 0.05 to 0.63). Worsening psychosis subsyndrome score was associated with partial insight into the COVID-19 situation (OR 9.57, 95% CI 1.14 to 80.71), reduced contact with the informal carer (OR 4.45, 95% CI 1.01 to 19.71), and impaired function as indicated by FAST (OR 2.59,

Table 1 Prepandemic characteristics for the 104 dyads (persons with dementia and informal carers, n)

	N=104
Person with dementia	
Age, mean (SD)	82 (7)
Female gender, n (%)	63 (61)
Residency	
Living alone, n (%)	46 (44)
Coresiding with the reporting informal carer, n (%)	46 (44)
Coresiding with someone else than the informal carer, n (%)	12 (12)
Dementia aetiology	
Alzheimer's disease, n (%)	45 (43)
Vascular dementia, n (%)	6 (6)
Dementia in other diseases classified elsewhere, n (%)	10 (10)
Unspecified dementia, n (%)	43 (41)
MMSE, range 0–30, median (IQR)	21(18–24)
FAST, range 1–7, median (IQR)	4 (4–4)
GMHR, range 1–4, median (IQR)	3 (2–3)
PSMS, range 6–30, median (IQR)	11 (9–14)
IADL, range 8–31, median (IQR)	22 (18–27)
Drugs in general	
Total number, median (IQR)	6 (4–8)
Regularly, median (IQR)	5 (3–7)
Psychotropic drugs	
Total no, median (IQR)	1 (0–2)
Regularly, median (IQR)	1 (0–1)
Antipsychotic drugs (N05A), n (%)	6 (6)
Anxiolytic drugs (N05B), n (%)	3 (3)
Hypnotic/sedative drugs (N05C), n (%)	10 (10)
Antidepressant drugs (N06A), n (%)	19 (18)
Antidementia drugs (N06D), n (%)	52 (50)
On-demand, median (IQR)	0 (0–0)
Antipsychotic drugs (N05A), n (%)	0 (0)
Anxiolytic drugs (N05B), n (%)	5 (5)
Hypnotic/sedative drugs (N05C), n (%)	12 (12)
Antidepressant drugs (N06A), n (%)	0 (0)
Antidementia drugs (N06D), n (%)	0 (0)
Volunteering services, n (%)	8 (8)
Healthcare services	
Daily home nursing, n (%)	52 (50)
Weekly day care, n (%)	29 (28)
Respite care (In-home and out-of-home), n (%)	2 (2)
Informal carer	
Age, mean (SD)	65 (12)
Female gender, n (%)	68 (65)
Kinship to the person with dementia	
Spouse, n (%)	44 (42)
Child, n (%)	58 (56)
Others, n (%)	2 (2)

Drugs were classified by the Anatomical Therapeutic Chemical Index; antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants and antidementia drugs constituted psychotropic drugs.
FAST, Functional Assessment Staging; GMHR, General Medical Health Rating Scale; IADL, Instrumental Activities of Daily Living Scale; ICD-10, International Classification of Diseases10th version; MMSE, Mini-Mental Status Examination; Prepandemic, Six-month assessment of parent trial (12 December 2019 to 11 March 2020); PSMS, Physical Self-Maintenance Scale.

95% CI 1.07 to 6.27). An inverse association occurred for higher dependency in activities of daily living by PSMS and worsening psychosis subsyndrome (OR 0.68, 95% CI 0.51 to 0.91). Worsening depressive symptoms was associated with impaired function by FAST (OR 4.96, 95% CI 1.57 to 15.65), in contrast to lower odds associated with Alzheimer's disease (OR 0.21, 95% CI 0.05 to 0.85) and psychotropic drug use on-demand (OR 0.16, 95% CI 0.03 to 0.75).

Post hoc analysis did not show any association between use of antipsychotic drugs before the restrictions and worsening psychosis subsyndrome using unequal variances t-test (online supplemental table A). Similarly, we found no association between use of antidepressants and worsening depressive symptoms. Neither randomisation

Table 2 Pandemic characteristics for the 104 persons with dementia (n) as perceived by their informal carers

	N= 104
Degree of insight	
Sufficient, n (%)	34 (33)
Partial, n (%)	54 (52)
To no degree, n (%)	16 (15)
Change in contact with the informal carer*	
Reduced, n (%)	29 (28)
No change, n (%)	49 (47)
Increased, n (%)	23 (22)
Ceased volunteering services*, n (%)	8 (8)
Change in healthcare services*, n (%)	42 (40)
Postponed or averted contacts with healthcare professionals*, n (%)	32 (31)

*Relative the prepandemic situation. Healthcare services provided by the municipality: home nursing services, home help, day-care and respite care (in-home and out-of-home).
Pandemic, PAN.DEM assessment (20 April 2020 to 15 May 2020).

Table 3 Prepandemic compared with pandemic behavioural and psychological symptoms for the 104 persons with dementia (n)

	Prepandemic			Pandemic			
	N (%) with symptom load of clinical relevance*	Median	IQR	N (%) with symptom load of clinical relevance*	Median	IQR	P value
Neuropsychiatric inventory (NPI-12)							
Total score, range 0–144		16	4.5–29		20	7–32.5	0.03†
Subsyndromes							
Psychosis‡, range 0–24		0	0–3		0.5	0–6	0.01†
Hyperactive behaviour§, range 0–60		5.5	0–12		4	0–12	0.79
Mood¶, range 0–48		6	0–12		6.5	1–12	0.21
Domain scores, range 0–12							
Delusions	20 (19)	0	0–2	31 (30)	0	0–6	0.04†
Hallucinations	8 (8)	0	0–0	16 (15)	0	0–0	0.23
Agitation	23 (22)	0	0–3	18 (17)	0	0–2	0.45
Depression	25 (24)	0	0–3	40 (38)	1	0–6	0.04†
Anxiety	18 (17)	0	0–2	31 (30)	0	0–4	0.07
Euphoria	8 (8)	0	0–0	4 (4)	0	0–0	0.19
Apathy	35 (34)	0	0–4	30 (29)	0	0–4	0.50
Disinhibitions	9 (9)	0	0–0	15 (14)	0	0–1.5	0.16
Irritability	28 (27)	0	0–4	29 (28)	0	0–4	0.78
Aberrant motor behaviour	23 (22)	0	0–1	24 (23)	0	0–2.5	0.66
Sleep disturbances	25 (24)	0	0–3	28 (27)	0	0–4	0.82
Appetite changes	14 (13)	0	0–1	17 (16)	0	0–1	0.84
No of BPSD with symptom load of clinical relevance*, range 0–12		2	0–4		3	1–5	<0.001†
Cornell Scale for Depression in Dementia (CSDD)							
Total score, range 0–38	34 (33)	5	3–9	41 (39)	7	4–12	0.01†

*NPI domain scores ≥4 indicate BPSD with symptom load of clinical relevance. CSDD total score ≥8 indicates depression of clinical relevance.
†Indicates two-tailed p<0.05.
‡ Psychosis: delusions and hallucinations
§ Hyperactive behaviour: agitation, euphoria, irritation, disinhibition, aberrant motor behaviour
¶ Mood: depression, apathy, sleep disturbances and appetite changes
BPSD, behavioural and psychological symptoms of dementia; P, p value for difference in median between time points by the Wilcoxon matched-pairs signed-rank test; Pandemic, PAN.DEM assessment (20 April 2020 to 15 May 2020); Prepandemic, Six-month assessment of parent trial (12 December 2019 to 11 March 2020).

to the intervention vs control of the parent trial showed associations with worsening NP-12 total score, psychosis subsyndrome nor depressive symptoms (online supplemental table A). To explore if consecutive sampling introduced bias, we compared our study sample to those not included yet still in parent trial at the prepandemic assessment, revealing minimal differences (online supplemental table B).

DISCUSSION

Our primary aim was to compare prepandemic and pandemic levels of BPSD in home-dwelling people with dementia during the two first months of COVID-19 restrictions in Norway. Even though BPSD fluctuates over the dementia course, our study indicates that the COVID-19 restrictions caused an overall increase in BPSD over a mean of 86 days, and that odds of worsening were four times higher with postponed or averted contacts with healthcare professionals. More specifically, the increase was most pronounced for symptoms of psychosis and depression. The odds for worsening psychosis increased 10-fold with partial insight into the COVID-19 situation and 4-fold with reduced contact with informal carers, while as-needed use of psychotropic drugs was associated with fewer depressive symptoms.

Strengths and weaknesses

Our study provides prospective data obtained shortly before and under the COVID-19 restrictions rated by the same informal carer for each subject and based on extensive assessor-blinded interviews with validated, well-established instruments.[12 13] We used established cut-off scores when presenting BPSD with symptom load of clinical relevance.[6 19] The parent trial population was recruited from different municipalities to be representative to the Norwegian demographic in terms of dementia aetiology, severity and symptomatology.[13] As our study

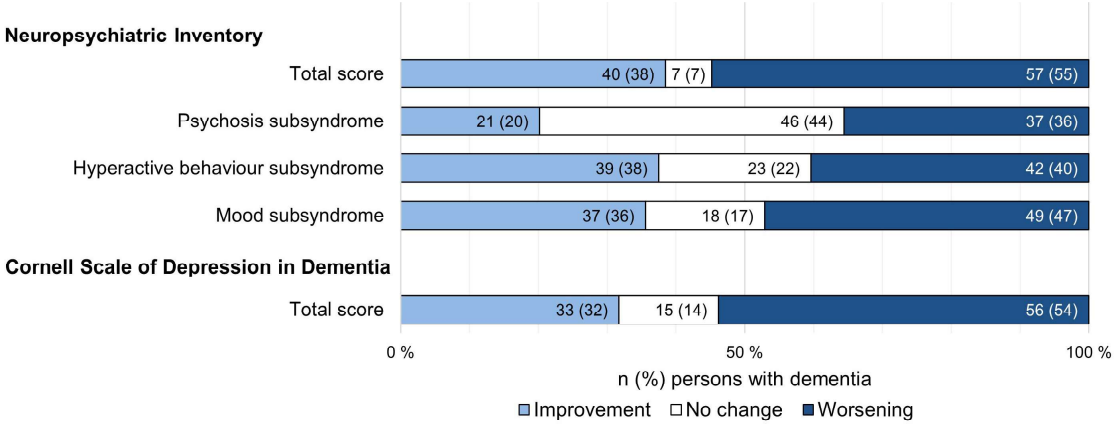


Figure 2 Change in behavioural and psychological symptoms in n (%) persons with dementia from the prepandemic to the pandemic assessment. n: 104. Prepandemic: Six-month assessment of parent trial (12 December 2019 to 11 March 2020). Pandemic: PAN.DEM assessment (20 April 2020 to 15 May 2020). Neuropsychiatric Inventory, subsyndrome score: psychosis (delusions and hallucinations), hyperactive behaviour (agitation, euphoria, irritation, disinhibition, aberrant motor behaviour), mood (depression, apathy, sleep disturbances and appetite changes). Cornell Scale for Depression in Dementia, total score.

sample was fairly similar to those dyads not included from the parent trial, we argue that our study was not biased by selection.

There are weaknesses to address. Despite efforts, we were not able to invite all potential respondents through consecutive sampling before the restrictions were eased for the first time, explaining the limited sample size. CSDD is not validated for telephone interviews[18] yet our findings using CSDD were consistent with the depression domain of NPI-12, which can be used as a telephone interview instrument.[16] Previous work has shown that carer psychosocial factors such as sense of competence, guilt and relationship quality account for up to 56% of the variance in BPSD-related distress.[26] In the case of the pandemic, stress-related symptoms were experienced by two-thirds of family carers soon after the outbreak hit Italy (N=4913) and were associated with incident or worsening BPSD.[9] The authors conclude that they could not determine whether increased BPSD were the cause or consequence of carer distress, as both counterparts were exposed to similar conditions during quarantine. Even though we did not assess such domains, these considerations apply to our study. Another point is that 28% of the informal carers reported reduced contact with the person with dementia, leaving them with less clinical observation. As 44% of the dyads were not living together, we suggest that some violated the restrictions to visit their loved ones and keep their obligations as careers, possibly mitigating the impact on BPSD. These weaknesses should be considered when interpreting the results, along with the wide CIs of the covariates associated with worsening BPSD. Notably, our data capture the impact of the initial phase of the outbreak in Norway and can therefore not answer longer-term consequences from either reimposition or lengthening of invasive restrictions.

Comparison with other studies

This study provides data on the negative mental health consequences of the COVID-19 restrictions for people with dementia. Using a non-randomised, non-controlled design to evaluate causations may be reasonable in the pandemic scenario as no other way of assessing the impact of the COVID-19 restrictions exist. However, our results should be interpreted with caution. The deterioration in BPSD could in theory be caused by the progression of the dementia syndrome itself, rather than being exacerbated by the pandemic restrictions. Arguing against this, change in BPSD over 4 months was substantially lesser in an observational cohort of nursing home residents of which the majority had dementia than what we demonstrate comparing prepandemic and pandemic symptom levels.[27]

Our findings echo a small body of the existing literature on this topic. A study from Spain noted increases in levels of agitation, apathy, and aberrant motor behaviour 5 weeks into lockdown in outpatients with mild cognitive impairment and Alzheimer's disease (N=40), but no increase in psychotic symptoms.[28] A cross-sectional study from Italy (N=139) describes exacerbation of psychotic symptoms in a small percentage of subjects with subjective cognitive decline, mild cognitive impairment and dementia.[29] This study, in part, used self-assessments, that may have led to underreporting of delusions and hallucinations. Even though other studies are equivocal on whether psychosis worsened,[8 9] UK registry data indicate higher antipsychotic prescription rates to people with dementia during the pandemic, and the authors speculate that this increase may be the result of worsened agitation and psychosis.[30] Meanwhile, our study revealed no associations between psychotropic drugs and psychosis, likely given that very few patients used antipsychotics

Table 4 Factors associated with worsening in behavioural and psychological symptoms of dementia from the prepandemic to the pandemic assessment

	NPI-12 total score				NPI-12 psychosis subsyndrome				CSDD total score			
		95% CI				95% CI				95% CI		
Covariates	OR	Lower	Upper	P value	OR	Lower	Upper	P value	OR	Lower	Upper	P value
Prepandemic characteristics												
Person with dementia												
Age	1.01	0.92	1.11	0.79	0.91	0.82	1.01	0.16	1.09	0.97	1.22	0.16
Female gender	0.51	0.13	1.98	0.34	0.36	0.09	1.52	0.09	0.19	0.03	1.31	0.09
Living alone	0.20	0.04	1.01	0.05	2.69	0.41	17.80	0.31	0.55	0.07	4.18	0.57
Alzheimer's disease*	0.18	0.05	0.63	0.01¶¶	0.84	0.23	3.08	0.79	0.21	0.05	0.85	0.03¶¶
MMSE†	1.19	1.01	1.40	0.04¶¶	0.97	0.82	1.14	0.68	0.96	0.80	1.15	0.65
FAST‡	0.98	0.45	2.16	0.97	2.59	1.07	6.27	0.04¶¶	4.96	1.57	15.65	0.01¶¶
IADL§	0.96	0.80	1.15	0.64	1.19	0.98	1.45	0.08	0.84	0.67	1.07	0.16
PSMS¶	1.00	0.79	1.28	0.99	0.68	0.51	0.91	0.01¶¶	0.99	0.76	1.29	0.96
GMHR**	0.91	0.36	2.32	0.84	2.06	0.72	5.88	0.18	0.84	0.28	2.50	0.76
Psychotropic drugs††												
Regularly	1.16	0.54	2.48	0.71	0.67	0.31	1.47	0.32	1.11	0.49	2.53	0.80
On-demand	0.35	0.09	1.46	0.15	2.95	0.69	12.66	0.15	0.16	0.03	0.75	0.02¶¶
Informal carer												
Age	0.97	0.92	1.03	0.40	1.04	0.98	1.12	0.21	0.99	0.93	1.06	0.87
Female gender	1.81	0.50	6.49	0.36	0.70	0.18	2.80	0.62	0.82	0.16	4.27	0.82
Pandemic characteristics, person with dementia												
Insight to the COVID-19 situation‡‡												
Partial	0.61	0.10	3.69	0.60	9.57	1.14	80.71	0.04¶¶	0.67	0.10	4.44	0.68
Sufficient	1.14	0.15	8.82	0.90	3.69	0.33	40.93	0.29	2.70	0.26	28.27	0.41
Contact with the informal carer§§												
Reduced	1.88	0.48	7.44	0.37	4.45	1.01	19.71	0.049¶¶	1.40	0.27	7.27	0.69
Increased	2.41	0.61	9.49	0.21	3.21	0.71	14.55	0.13	0.30	0.07	1.23	0.10
Ceased volunteering services	0.30	0.04	2.24	0.24	0.20	0.02	2.11	0.18	0.59	0.04	7.91	0.69
Change in healthcare services	0.48	0.13	1.78	0.28	0.48	0.11	2.08	0.33	1.16	0.28	4.83	0.84
Postponed or averted contacts with healthcare professionals	3.96	1.05	14.95	0.04¶¶	1.55	0.45	5.42	0.49	3.37	0.70	16.08	0.13

Change dichotomised into worsening/not worsening. OR explored by multiple logistic regression, estimates adjusted for all other factors in the models.
*Alzheimer's disease, reference: all other dementia aetiologies.
†MMSE, range 0–30, higher scores indicate better cognition, reference: 30.
‡FAST, range 1–7, lower scores indicate better functioning, reference: 1.
§IADL, range 8–31, lower scores indicate better functioning, reference: 8.
¶PSMS, range 6–30, lower scores indicate better functioning, reference 6.
**GMHR, range 1–4, lower score indicate higher comorbidity burden, reference 4.
††Number of psychotropic drugs according to the Anatomical Therapeutic Chemical Index: antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A) and anti-dementia drugs (N06D), reference: 0.
‡‡Degree of insight into the COVID-19 situation as perceived by the informal carer, reference: no insight.
§§Change in contact with the informal carer, reference: no change.
¶¶P: two-tailed p<0.05
CSDD, Cornell Scale of Depression in Dementia ; FAST, Functional Assessment Staging, at inclusion; GMHR, General Medical Health Rating Scale; IADL, Instrumental Activities of Daily Living Scale; MMSE, Mini-Mental Status Examination, at inclusion; n, 89 dyads (person with dementia and informal carer); NPI-12, Neuropsychiatric Inventory, twelve item version, with psychosis subsyndrome constituting delusions and hallucinations; Pandemic, PAN.DEM assessment (20 April 2020 to 15 May 2020); Prepandemic, Six-month assessment of parent trial (12 December 2019 to 11 March 2020); PSMS, Physical Self-Maintenance Scale.

before the pandemic, in addition to the lack of real-time prescription data throughout the outbreak. Because this is a nascent area of research, discrepancies may be attributed to heterogeneity in design, as well as dementia severity and aetiology.

Early findings suggest that older adults at group level are more resilient to the mental health effects of the pandemic than younger ones.[11] Nonetheless, our study adds to the cross-sectional reports calling attention to deteriorating depressive symptoms among people with dementia.[8–10] For better communication within and between dyads and their formal caregivers, digital devices may enhance individual support.[12] Further, anxiolytics and hypnotics/sedatives were associated with fewer depressive symptoms when used as-needed in our sample. These drugs are known to temporarily alleviate some

of the symptoms assessed by the CSDD, such as anxiety, irritability and agitation. However, in line with national guidelines, we rather recommend that antidepressants are considered if severe symptoms persist.[31]

Our study supports the WHO's concerns that the pandemic would negatively impact the mental health of people with cognitive impairments.[5] Even though way of life varies globally, the policies implemented in response to COVID-19 are likely equally disruptive to the environment of home-dwelling people with dementia across nations.[3] We, therefore, argue that our findings are generalisable to other countries. Furthermore, they emphasise that non-pharmacological approaches still should be the first-line treatment to avoid BPSD deterioration regardless of context.

Unanswered questions and future research

Future research should explore the long-term impact of the COVID-19 restrictions on BPSD, and whether moderations or service innovations can mitigate worsening. Less than 5% of trials on COVID-19 involve behavioural and mental health interventions,[32] emphasising the need for knowledge to adapt restrictions and navigate the unforeseeable consequences for persons with dementia and informal caregiver of the current, and future, pandemics.

Author affiliations
[1]Haraldsplass Deaconess Hospital, Bergen, Norway
[2]Centre for Elderly and Nursing Home Medicine, Department of Global Public Health Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway
[3]Bergen Municipality, Bergen, Norway
[4]McLean Hospital, Belmont, Massachusetts, USA
[5]Harvard Medical School, Boston, Massachusetts, USA
[6]Section for Epidemiology and Medical Statistic, Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway
[7]Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway
[8]NKS Olaviken Gerontopsychiatric Hospital, Askøy, Norway

Acknowledgements Renira Angeles (postdoctoral fellow, NORCE) and Nathalie Puaschitz (postdoctoral fellow, Western Norway University of Applied Sciences) contributed to data collection. Rune Samdal secured public and patient involvement. The motivation and willingness of dyads and municipal personnel in Bergen, Bærum and Kristiansand made this study possible.

Contributors BSH was primary investigator. MHG, BSH, MV and LIB designed and planned the study. MHG, MV and LIB collected data. MHG did the data analysis, supervised by JM. MHG and LIB wrote the first draft of the manuscript. MHG, BSH, IVV, JM, MV, MN and LIB were actively involved in interpreting the results, revising the manuscript and approving the final version. LIB is responsible for the overall content as guarantor. The corresponding author attests that all listed authors meet the authorship criteria and that no others fulfilling authorship criteria are omitted.

Funding This work was supported by the Research Council of Norway (grant number 273581). The Norwegian Government and the G.C. Rieber Foundation supports the Centre for Elderly and Nursing Home Medicine, University of Bergen, organising the conduction of LIVE@Home.Path and PAN.DEM. The research was designed, conducted, analysed, interpreted and written by the authors independently of the funding sources. All authors had access to the data in the study and can take responsibility for the integrity of the data and the accuracy of data analysis.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: MHG, MV, JM and LIB had financial support from the Research Council of Norway (grant number 273581), for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; IVV reports receiving honorarium as editor of the American Journal of Geriatric Psychiatry.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Regional Committee for Medical and Health Research Ethics North Norway (reference number 2019/385 for the parent trial and 10861 for PAN.DEM).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Relevant anonymised data are available at reasonable request. Data are fully available to collaborators and affiliated researchers.

ORCID iD
Marie H Gedde http://orcid.org/0000-0002-8423-6402

REFERENCES

1 Atkins JL, Masoli JAH, Delgado J, *et al*. Preexisting comorbidities predicting COVID-19 and mortality in the UK Biobank community cohort. *J Gerontol A Biol Sci Med Sci* 2020;75:2224–30.
2 Suárez-González A, Livingston G, Low L-F. Impact and mortality of COVID-19 on people living with dementia: cross-country report, 19 August 2020. Available: https://ltccovid.org/wp-content/uploads/2020/08/International-report-on-the-impact-of-COVID-19-on-people-living-with-dementia-19-August-2020.pdf [Accessed Aug 2021].
3 Islam N, Sharp SJ, Chowell G, *et al*. Physical distancing interventions and incidence of coronavirus disease 2019: natural experiment in 149 countries. *BMJ* 2020;370:m2743.
4 Wang H, Li T, Barbarino P, *et al*. Dementia care during COVID-19. *Lancet* 2020;395:1190–1.
5 World Health Organization. Mental health and psychosocial considerations during the COVID-19 outbreak. Available: https://apps.who.int/iris/handle/10665/331490 [Accessed 18 Mar 2020].
6 Vik-Mo AO, Giil LM, Borda MG, *et al*. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. *Br J Psychiatry* 2020;216:43–8.
7 Bessey LJ, Walaszek A. Management of behavioral and psychological symptoms of dementia. *Curr Psychiatry Rep* 2019;21:66.
8 Cohen G, Russo MJ, Campos JA, *et al*. COVID-19 epidemic in argentina: worsening of behavioral symptoms in elderly subjects with dementia living in the community. *Front Psychiatry* 2020;11:866.
9 Cagnin A, Di Lorenzo R, Marra C, *et al*. Behavioral and psychological effects of coronavirus disease-19 quarantine in patients with dementia. *Front Psychiatry* 2020;11:578015.
10 El Haj M, Altintas E, Chapelet G, *et al*. High depression and anxiety in people with Alzheimer's disease living in retirement homes during the covid-19 crisis. *Psychiatry Res* 2020;291:113294.
11 Vahia IV, Jeste DV, Reynolds CF. Older adults and the mental health effects of COVID-19. *JAMA* 2020;324:2253–2235.
12 Gedde MH, Husebo BS, Erdal A, *et al*. Access to and interest in assistive technology for home-dwelling people with dementia during the COVID-19 pandemic (PAN.DEM). *Int Rev Psychiatry* 2021;33:404–11.
13 Husebo BS, Allore H, Achterberg W, *et al*. LIVE@Home.Path—innovating the clinical pathway for home-dwelling people with dementia and their caregivers: study protocol for a mixed-method, stepped-wedge, randomized controlled trial. *Trials* 2020;21:1–16.

14 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.
15 Reisberg B. Functional assessment staging (FAST). *Psychopharmacol Bull* 1988;24:653–9.
16 Cummings J. The neuropsychiatric inventory: development and applications. *J Geriatr Psychiatry Neurol* 2020;33:73–84.
17 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.
18 Alexopoulos GS, Abrams RC, Young RC, *et al*. Cornell scale for depression in dementia. *Biol Psychiatry* 1988;23:271–84.
19 Barca ML, Engedal K, Selbaek G. A reliability and validity study of the Cornell scale among elderly inpatients, using various clinical criteria. *Dement Geriatr Cogn Disord* 2010;29:438–47.
20 Selbaek G, Kirkevold O, Sommer OH, *et al*. The reliability and validity of the Norwegian version of the neuropsychiatric inventory, nursing home version (NPI-NH). *Int Psychogeriatr* 2008;20:375–82.
21 Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–86.
22 Lawton MP. Aging and performance of home tasks. *Hum Factors* 1990;32:527–36.
23 Lyketsos CG, Galik E, Steele C, *et al*. The general medical health rating: a bedside global rating of medical comorbidity in patients with dementia. *J Am Geriatr Soc* 1999;47:487–91.
24 World Health Organization. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva, Switzerland, 1992.
25 World Health Organization Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. ATC/DDD index, 2015. Available: https://www.whocc.no/atc_ddd_index/
26 Feast A, Orrell M, Russell I, *et al*. The contribution of caregiver psychosocial factors to distress associated with behavioural and psychological symptoms in dementia. *Int J Geriatr Psychiatry* 2017;32:76–85.
27 Gedde MH, Husebo BS, Mannseth J, *et al*. Less is more: the impact of deprescribing psychotropic drugs on behavioral and psychological symptoms and daily functioning in nursing home patients. results from the cluster-randomized controlled Cosmos trial. *Am J Geriatr Psychiatry* 2021;29:304–15.
28 Lara B, Carnes A, Dakterzada F, *et al*. Neuropsychiatric symptoms and quality of life in Spanish patients with Alzheimer's disease during the COVID-19 lockdown. *Eur J Neurol* 2020;27:1744–7.
29 Canevelli M, Valletta M, Toccaceli Blasi M, *et al*. Facing dementia during the COVID-19 outbreak. *J Am Geriatr Soc* 2020;68:1673–6.
30 Howard R, Burns A, Schneider L. Antipsychotic prescribing to people with dementia during COVID-19. *Lancet Neurol* 2020;19:892.
31 The Norwegian Directorate of Health. Nasjonal faglig retningslinje for demens [National professional guidelines on dementia], 2020. Available: https://www.helsedirektoratet.no/retningslinjer/demens [Accessed 4 Sep 2021].
32 Jones CW, Woodford AL, Platts-Mills TF. Characteristics of COVID-19 clinical trials registered with ClinicalTrials.gov: cross-sectional analysis. *BMJ Open* 2020;10:e041276.

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 9788230863121 (print)
9788230847695 (PDF)