End of life care in nursing homes

Palliative drug prescribing and doctors' existential vulnerability

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Countless conversations and philosophical musings with my mother and father have formed me. Crucially, in the midst of analysis in the spring of 2015, my father became ill with bile duct cancer, and lived for a little more than two months after diagnosis. He lived in Spain, his birth country, and enjoyed morning walks to the local cafeteria, where he'd have a breakfast of croissant and coffee in the warm shadow of orange trees, and the familiar sounds of his mother tongue. However, he had little family to care for him there. Home care services, a hospice or a decent nursing home were lacking. And so, three weeks before he died, he expressed in despair from his hospital bed a wish to come to Norway. A move I had insisted he make for several weeks, to ensure dignified care for him in his last days, close to his remaining family. He spent a precious last two weeks in a nursing home in Bergen, and I witnessed and shared his last days and hours and breaths of life. My own vulnerability bare, and the impermanence of existence so palpably reminded, the concept of existential vulnerability felt very real when suggested by Margrethe.

I dedicate this thesis to my father.

Abstract

Nursing homes are the main arena for end-of-life (EOL) care in Norway. Patients, their informal caregivers and academics alike have called for doctors more involved in EOL care, but the nursing home doctor's role has been given relatively little attention in research.

This thesis explores the doctor's work with EOL care in nursing homes from the perspectives of EOL prescription changes (paper I); the effectiveness and safety of palliative prescriptions (paper II); and from nursing home doctors' own experiences and how their existential vulnerability impacts on their work (paper III).

Paper I

Methods. A historical cohort study, set in three urban nursing homes in Norway, between January 2008 and February 2013. Drug prescriptions, diagnoses, and demographic data were collected from electronic patient records.

Results. 524 patients were included. On the day of death, almost all patients had active prescriptions; around three out of four patients were prescribed palliative drugs. Palliative drugs were associated with nursing home, length of stay >16 months, age, and a diagnosis of cancer. Initiations of palliative drugs and withdrawals of curative/preventive drugs most commonly took place on the day of death.

Paper II

Methods. A systematic search of the literature published before December 2016, including studies on safety or effectiveness of drug therapy in dying adults with at least one outcome on symptom control, adverse effects, or survival.

Results. Of 5940 unique titles identified, 12 studies met the inclusion criteria. Five studies assessed anticholinergics for death rattle, providing no evidence that scopolamine hydrobromide or atropine were superior to placebo. Five studies examined drugs for dyspnea, anxiety, or terminal restlessness, providing some

evidence supporting the use of morphine and midazolam. Two studies examined opioids for pain, providing some support for morphine, diamorphine and fentanyl. Eight studies included safety outcomes, revealing no important differences in adverse effects between the interventions, and no evidence for midazolam shortening survival.

Paper III

Methods. A qualitative study based on three focus group interviews with purposive samples of 17 nursing home doctors. The interviews were audio-recorded, transcribed, and analyzed with systematic text condensation (STC).

Results. Nursing home doctors interviewed in paper III experienced having to balance treatment compromises in order to assist patients' and families' preparation for death, with their sense of professional conduct. This was an arduous process demanding patience and consideration. Existential vulnerability also manifested as powerlessness mastering issues of life and death and families' expectations. Personal commitment was balanced with protective disengagement on the patient's deathbed, triggering both feelings of wonder and guilt.

Conclusion

Palliative drug therapy and drug therapy changes are common for nursing home patients on the last day of life. Improvements in end-of-life care in nursing homes imply addressing prognostication and an earlier response to palliative needs.

There is a lack of evidence concerning the effectiveness and safety of palliative drug treatment in dying patients, and the reviewed evidence provides limited guidance for clinicians. Anticholinergic agents are not supported for the treatment of death rattle.

Existential vulnerability is experienced by nursing home doctors as a burden of powerlessness and guilt in difficult treatment compromises and in the need for protective disengagement, but also as a resource in communication and professional coping.

Sammendrag på norsk

Sykehjem er den fremste arena for terminalomsorg i Norge. Legens økte involvering i terminalomsorgen er etterspurt av pasientene, deres omsorgspersoner, og fagmiljøet, men har fått relativt liten oppmerksomhet i forskning.

Denne avhandlingen utforsker sykehjemslegens arbeid i terminalomsorgen, fra tre forskjellige perspektiv: legemiddelendringer på sykehjem ved livets slutt (artikkel I), evidens for nytte og sikkerhet ved lindrende legemidler ved livets slutt (artikkel II), og sykehjemslegens egne erfaringer, og hvordan deres eksistensielle sårbarhet påvirker deres arbeid.

Artikkel I

Metode. En historisk kohort studie, gjennomført ved tre by-sykehjem i Norge, i perioden januar 2008 til februar 2013. Legemiddelforskrivninger, diagnoser, og demografiske data ble innsamlet fra elektronisk pasientjournal.

Resultat. 524 pasienter ble inkludert. På dødsdagen hadde nær alle pasienter aktive legemiddel-forskrivninger; omkring 3 av 4 sto på lindrende legemidler. Lindrende legemidler var forbundet med sykehjem, oppholdsvarighet over 16 måneder, alder, og kreftdiagnose. Flest endringer av lindrende legemidler og seponeringer av kurativ/preventive legemidler skjedde på dødsdagen.

Artikkel II

Metode. Systematisk litteratursøk av publikasjoner frem til desember 2016 på effektivitet og sikkerhet av legemiddelbehandling av døende voksne pasienter med minst ett utfallsmål innen symptomkontroll, bivirkning eller overlevelse.

Resultater. Av 5940 unike titler identifisert, møtte 12 inklusjonskriteriene. Fem studier omhandlet antikolinerge legemidler for dødsralling, og viste ingen evidens for at skopolamin hydrobromid eller atropin var bedre enn placebo. Fem studier undersøkte legemiddelbehandling av tungpust, angst, og terminal rastløshet/uro, og viste noe

støtte for bruken av morfin og midazolam. To studier undersøkte opiater for smerte, og viste noe støtte for morfin, heroin, og fentanyl. Åtte studier undersøkte legemiddelsikkerhet, og viste ingen nevneverdige forskjeller i bivirkninger mellom intervensjoner, og uendret overlevelse ved bruk av midazolam.

Artikkel III

Metode. En kvalitativ studie basert på tre fokusgruppeintervju med strategisk utvalg av 17 sykehjemsleger. Intervjuene ble tatt opp, transkribert, og analysert med systematisk tekstkondensering.

Resultater. Sykehjemslegene erfarte å balansere behandlingskompromisser for behjelpe pasient og pårørendes forberedelse til døden, med deres egen profesjonalitet. Dette var en prosess som krevde tålmodighet og omtanke. Eksistensiell sårbarhet ble også uttrykt som maktesløshet i å mestre liv og død, og pårørendes forventninger til legen. På pasientens dødsleie ble personlig nærhet avveid mot beskyttende distanse, og kunne utløse følelser både av skyld og ærefrykt.

Konklusjon

Lindrende legemiddelbehandling og endringer i legemidler er vanlige ved livets slutt for sykehjemspasienter. Forbedringer i terminalomsorgen innebærer bedre prognostisering av døden, og en tidligere respons på palliative behov.

Det er mangel på evidens for effekt og sikkerhet av lindrende legemiddelbehandling av døende pasienter, og gjennomgått evidens alene gir lite veiledning for klinikere. Antikolinerge medikamenter støttes ikke for behandling av dødsralling.

Eksistensiell sårbarhet erfares av sykehjemsleger både som en byrde av maktesløshet og skyldfølelse ved vanskelige behandlingskompromiss, og i behovet for beskyttende distanse fra pasientsituasjoner, men også som en ressurs i kommunikasjon og profesjonell mestring.

List of publications

Paper I - Jansen K, Schaufel MA, Ruths S. Drug treatment at the end of life: an epidemiologic study in nursing homes. Scand J Prim Health Care. 2014;32:187-92.

Paper II - Jansen K, Haugen DF, Pont L, Ruths S. Safety and effectiveness of palliative drug treatment in the last days of life - a systematic literature review. Accepted for publication in J Pain Symptom Manage.

Paper III - Jansen K, Ruths S, Malterud K, Schaufel MA. The impact of existential vulnerability for nursing home doctors in end-of-life care: A focus group study. Patient Educ Couns. 2016;99:2043-2048.

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Contents

Abbreviations

ACP	Advance care planning
AOR	Adjusted odds ratio
CI / KI	Confidence interval / konfidensintervall (norsk)
EOL	End of life
EPHPP	Effective Public Health Practice Project
EPR	Electronic patient record
GBD	Geriatrisk Basis Datasett
ICD-10	International Classification of Diseases, 10th revision
LTC	Long-term care
NICE	The National Institute for Health and Care Excellence
RCT	Randomized controlled trial
STC	Systematic text condensation
WHO	World Health Organization

1. Introduction

1.1   The concepts of palliative care, end of life, and dying

The World Health Organization (WHO) defined palliative care in 2002 as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1] Closely resembling the WHO definition of 1990, palliative care is defined by the European Association of Palliative Care as "... the active, total care of the patient whose disease is not responsive to curative treatment." [2]

In contrast to these standardizations of the palliative care concept, various and inconsistently defined terms are used in the palliative care literature to refer to the dying stages of illness or the last period of life. Several reasons have been proposed to explain this, such as the multidisciplinary nature of palliative care, the common euphemisms surrounding death and dying, and regional variations in the structures and processes of palliative care programs. [3]

Confusing inconsistencies surround in particular the time period meant in concepts such as "end of life" (EOL), "terminal care", "dying" and "actively dying", referring to everything from hours to several years. [4] Speaking in specific time frames such as months, weeks, or days has therefore been recommended when communicating with patients about their prognosis. [5, 6] For research purposes, two different approaches may be used in defining the dying stages, depending on whether the term is defined prospectively or retrospectively: 1) a survival prognosis based on the clinical judgement of irreversible decline of physiological function before death, or 2) retrospectively ascertained time from study observation to death.

A 2014 systematic review of the definitions of these terms used in the research literature, textbooks, dictionaries and palliative organization websites, found that the terms "end of life", "terminally ill", and "terminal care" share a similar meaning:

progressive life-limiting disease with a prognosis of months or less. (4) The same review found that the term "actively dying" specifically relates to the last hours and days of life but is seldom used in the literature.

EOL care is generally defined as palliative care provided at the EOL, while palliative care extends all the way from the point of diagnosis of a life-threatening condition. (7) EOL care is therefore more appropriate where care concerns an expected end to life from old age such as commonly is the case in nursing homes. EOL and EOL care may be used in a wide definition of the last two years, and a narrow definition of the last few hours or days of life. (2) Although this distinction may not always be needed, this thesis generally adheres to the narrow meaning of the word.

1.2   EOL care in Norwegian nursing homes

Of the approximately 40,000 people that died in 2015, 48 % died in a nursing home, whereas 31% died in a hospital and 14% at home. (8) This makes nursing homes the most common setting for EOL care in Norway.

Care at long-term care (LTC) wards in nursing homes implies EOL care in the wide sense - patients deceased here reside on average only two years before dying. And while the older population in Norway is generally becoming healthier, nursing homes are home to the very frailest, and increasingly so. (9, 10) Nursing home patients to a greater extent than ever have complex health problems and functional impairment, requiring more medical and nursing services. Nursing home patients in Norway are on average 84.1 years old. Around 70% are women, who are on average are 5 years older than men. Around 80% are in long-term stays, 80% have significant need for assistance, (10) and 80% have some degree of dementia. (11)

While some nursing homes have dedicated palliative beds, specialized palliative services are generally offered by multidisciplinary teams in palliative care units and outpatient clinics in hospitals. By March 2017, there were 40 specialized palliative care units in Norway, 42 municipal palliative care units (nursing homes with more than four dedicated palliative beds), and 99 municipal nursing homes with (less than

four) dedicated palliative beds. (12)

In terms of resources in an international perspective, Norway gives high priority to elderly care and LTC facilities, with relative national health expenditures on LTC facilities comparable mainly to the Netherlands, Switzerland, Belgium, Denmark, and Sweden. (13)

All health care personnel treating dying patients, both in municipally-governed primary care such as nursing homes and home care, and in state-governed secondary and tertiary care, are expected to offer basic palliative care services to any patients in need, implying satisfactory symptom control and care at the EOL according to the WHO principles of palliative care, (1) as well as knowledge of when to refer the patient to specialized services, and preferably hosting an advanced practice registered nurse (*ressursykepleier*). (14) Most nursing home staff have professional or vocational training such as registered nurses, nursing assistants, physiotherapists and occupational therapists.

Nursing home doctors in Norway are a blend of general practitioners providing a part-time service and, increasingly, dedicated nursing home doctors commonly working at larger nursing homes. Since 2012, an "Area of Competence" (*Kompetanseområde*) for Elderly and Nursing Home Medicine has been available for certification, building upon the specialties of general practice, internal medicine, geriatrics, neurology, or physical and rehabilitation medicine. (15) Similarly, there is no specialty of palliative medicine in Norway, but since 2011, an Area of Competence as a training program and certification building on any other clinical specialty. (16)

Nursing home doctors in Norway and the Netherlands find inadequate staffing levels, lack of competence, time, and interest as important barriers to quality EOL care. (17) Nevertheless, newly qualified doctors in Norway find considerable opportunity in nursing homes for training in patient and family dialogues, complex decision-making and interdisciplinary work. (18)

1.3   Working for a "good death" – the tasks of the nursing home doctor

According to nurses, a dignified death in LTC facilities means treating patients with respect, helping them prepare for the EOL, promoting shared decision-making, and providing high-quality care. (19) According to relatives of LTC residents with dementia, patients' optimistic attitude, physical and psychological distress, and facility characteristics are associated with dying peacefully, (20, 21) and quality of life is associated with age, functional status, dementia severity, pain, psychiatric disorders, pulmonary diseases and neuropsychiatric symptoms. (22)

Efforts to define a good death point to some key tasks in EOL care for the nursing home staff: symptom management, communication and knowledge of preferences for care, a focus on quality of life, and taking care of the family. (23) The nursing home doctor has a central role in these tasks, the domains of which are addressed in the following sections.

Distress relief

Dying patients in nursing homes often have physical distress and need for symptomatic relief. (24) Common symptoms across care settings in the last two weeks of life death are dyspnea, weakness, respiratory secretions and pain. (25) A large Swedish nursing home register study found pain in the last week of life in almost 60% of patients, followed in order of prevalence by death rattle, anxiety, confusion, dyspnea (breathlessness) and nausea. (26) A longitudinal study in Norwegian nursing homes found that fatigue, drowsiness, and poor appetite were the most common symptoms on the day of death. (27) In another study on LTC patients in their last 8 hours of life, dyspnea, pain and noisy breathing were most common. (28)

For the dying phase, palliative care guidelines consistently recommend parenteral pharmacological symptom relief options such as opioids for pain or dyspnea, benzodiazepines for dyspnea, anxiety or delirium, antipsychotics for terminal delirium and agitation, and antimuscarinic anticholinergics for respiratory secretions. (14, 29-37)

The 2015 NICE guidelines on Care of dying adults in the last days of life (30) reviewed comparative studies on symptomatic drug treatment in the last 14 days of life. The NICE guidelines report one study on drug treatment of pain, three studies on breathlessness, three studies on nausea, and eight studies on respiratory tract secretions. However, for the treatment of other common symptoms in dying persons, such as anxiety, delirium or agitation no evidence is provided in the NICE guidelines nor in two earlier Cochrane reviews on a broader palliative care population. (38, 39)

As a precondition for responding to the need for symptomatic relief and the changing priorities of care as the patient approaches death, staff must also have a concept of remaining life-expectancy, and the ability to identify that the patient is actively dying. (40) This issue will be further addressed in the discussion section.

Deprescribing

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", (41) and involves identifying and balancing existing or potential harms to benefits within the context of an individual patient's life expectancy, care goals, level of functioning, values and preferences. (42) As death approaches, these goals and balances will change: preventive drugs will lose relevance, and palliative drugs gain in kind. (43-45)

Nursing home patients are commonly prescribed many drugs (polypharmacy) for numerous illnesses (multimorbidity) and ailments. Patients in Norwegian nursing homes take an average of six to seven different daily regular medications. (46-48). Polypharmacy is associated with drug-related problems such as adverse drug reactions, drug-drug interactions, functional decline, cognitive impairment and falls. (49-51) In nursing home patients with advanced dementia, it is also associated with increased mortality,(52) and hospital readmissions. (53-56)

Few rigorous studies have been conducted on deprescribing in the context of life-limiting illness and dying patients, but show that patients in all care settings continue to receive medications that are not prescribed for symptomatic treatment, that limited

evidence exists on the safety and efficacy of drugs, and that prescribing guidelines lack. (44, 57) Despite a growing interest in research on deprescribing in nursing homes, (58) nursing home patients are particularly underrepresented in clinical trials, further hindering the production of evidence to support guidelines in this population. (59, 60)

Advance care planning

Since what represents a good death differs between individuals, shared decision-making regarding treatment, recognizing the differences in values and preferences of patients and their families is needed. (61) Such conversations with patient and family adjusting aims of treatment and care are referred to as Advance care planning (ACP).

Rather than necessarily resulting in written treatment directives, sometimes referred to as "advance directives" or "physician/medical treatment orders" (see below), ACP can be regarded as a process supporting the shared decision-making between doctor, patient and family. (62) In a recent consensus statement, ACP is defined as follows: "Advance care planning is a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The goal of advance care planning is to help ensure that people receive medical care that is consistent with their values, goals and preferences during serious and chronic illness." (25) While ACP may be initiated in various ways, (63-66) the doctor in charge of treatment must take the main responsibility and initiative. In Norway, family and doctor participate in ACP conversations but, likely due to lack of cognitive ability, only sometimes the patient. (66-68) ACP is more likely to be done in nursing homes with good availability of doctors. (66).

Treatment orders / advance directives

Do-not-resuscitate orders, physician treatment orders for life-sustaining treatments, palliative care consultations, and multi-strategy interventions can help reduce hospital transfers from LTC facilities. (69-74) However, formalized physician treatment orders may be difficult to understand, interpret and explain, and are often based on limited discussions between doctors, patient and family. (72, 75, 76) Difficulties predicting the

impact of an illness and its treatment on future subjective well-being are likely to hinder such directives. (75, 77, 78) Complex ACP interventions may be more effective in meeting patients' preferences than such written orders alone. (79) Both the ACP process at large and treatment orders in particular, nevertheless represent a shift in treatment goals from a life-extending curative/preventive treatment perspective, to a palliative care approach focusing on the immediate quality of life. Palliative care approaches in nursing homes have shown to improve care, reduce hospitalizations and costs, and improve family members' perception of care. (80-84)

Relating to the "extended patient" of nearest family

Considering the value of relatives in aiding proxy assessments, in supporting the patient, in being important to the patient, but also themselves suffering from the patient's deterioration and dying, (85-88) the nursing homes doctor and staff must not only treat the patient, but the "extended patient" or "unit of care" that extends to the closest family and friends. (89) The majority of nursing home patients and relatives in Norway appreciate talking about EOL care, and want to be involved in decision-making. (67) Better communication with both patient and family members is associated with fewer in-hospital deaths and transfers to hospice, (90) improved patient comfort, (91) and reduced family stress. (92) Proxy assessors, including both relatives and professional carers, provide an indispensable insight into the nursing home patient perspective when he or she is too ill or cognitively impaired to answer for him-/herself. However, the views of patients and relatives may differ. Proxies are more likely to agree with patient responses on concrete, observable symptoms, patient functioning and service provision than on more subjective symptoms and experiences, leading for example to an overestimation of pain, and attenuation of self-reports toward moderate scores. (23, 93) While patients and relatives also differ in views on decision-making, patients trust relatives and staff to make important decisions for them. (94)

Unnecessary relocations

As part of decision-making regarding potentially burdensome life-prolonging

treatment, another important goal of care and task for the doctor is to avoid unnecessary transfers and relocations. (95) Hospital transfers for palliative care benefit the nursing home patient only if care is insufficient at the nursing home. (96) Care transitions or relocations between nursing home and hospital or emergency department are common, and represent a significant burden to the patient and relatives at the EOL, in particular in patients with dementia. (71, 97-99) In Norway, large differences in admission rates between institutions in the same municipality have been shown, pointing to a potential for reduction of unnecessary admissions. (100-102) Infections, fractures and cardiovascular disease are the most common reasons for admission. (100, 101)

In summary, the nursing home doctor must consider prognosis and engage in ACP dialogue with patient and family both as part of, and prerequisite to, treatment decision-making. How nursing home doctors relate to and execute these tasks, however, and the doctor's own perceptions of role and challenges as part of the EOL care team, is not answered by a simple list of tasks, and deserves investigation. This thesis investigates prescription changes in dying nursing home patients, (paper I) examines the evidence base for palliative drug prescriptions in the dying, (paper II) and explores nursing home doctors' experiences of working with dying patients. (paper III)

1.4   The nursing home doctors' experiences of EOL care

Palliative care is no doubt a team effort. (1) The perspectives of family members, care providers, and experts alike are integrated in models of care. (23) As one can expect, however, care team members´ perceptions regarding EOL care in the LTC setting differ. (61, 103) For example, nursing aides have been found to perceive more patient pain at the EOL compared to doctors or nurses, and doctors' perceptions of emotional support provided to families are lower than those of aides or nurses. (104) Doctors' experiences naturally also differ from family members'. Doctors perceive higher-quality aspects of nursing care and outcome, better consensus between staff and family on treatment, and a more peaceful death than family members. (105) While doctors,

nurses and relatives agree on many aspects of EOL decision-making for nursing home patients with dementia, relatives attach more importance to advance directives than doctors, and have more permissive attitudes towards hastening death. (106)

Nursing home patients and their relatives clearly want doctors more involved in EOL care and ACP discussions (67, 107-109) Family caregivers want face-to-face meetings with doctors about health changes, especially in the actively dying. (110) A stronger involvement by nursing homes in palliative care has also been called for by academics. (111)

We should expect time spent with the patient to be correlated with personal and emotional involvement, and burden of care. Closest to the patient is family, whose experiences and burden have been extensively studied. (112-114) Next, nursing staff in LTC will typically spend time with fewer patients than doctors, more time per patient, and get to know patients in an intimate setting of personal hygiene and daily informal conversation to which the doctor has less access. Perhaps therefore, relative to the patient, family and nursing staff perspectives, doctor's experiences with dying nursing home patients have been infrequently investigated. Nevertheless, doctors, far from stereotypes of objective and aloof clinicians, may still have close meetings with patients, and will have psychological responses to their experiences. In order to better understand doctors' important and sought-after contribution to improving EOL care in nursing homes, their voices must be heard.

Of note, Bern-Klug has interviewed nursing home doctors, finding that they consider consensus with the patient, family and other staff about the patient's status and an appropriate care plan to be important aspects of good EOL care. (115) Doctors also feel their work provides positive relationships, meaningful patient care, and autonomy; but difficult staff turnover, expectations, and administrative issues. (116) Other research has primarily focused on nursing home doctor's experiences with ACP (63, 65, 68, 106, 117, 118), and euthanasia (76, 119-121), the latter subject being outside the scope of this thesis.

This thesis promotes the nursing home doctor's perspective of role in EOL care not only indirectly by a focus on drug treatment at the EOL (paper I and II), for which the doctor is primarily responsible, but directly by exploring nursing home doctor's own experiences (paper III).

1.5   The doctor's existential concerns

The existential perspective is a natural one to bring up in the setting of nursing homes, where existence is threatened by illness, loss of function, and the prospect of death. The existential perspective is closely related to the spiritual perspective but need not be religious, and while existential concerns may be discussed in psychological terms, they need not amount to psychiatric disorders like depression. (122)

Normally, existential concerns in palliative care literature revolves around the patient, the protagonist of illness and death, searching for purpose and meaning to suffering (122, 123) Common themes of concern to terminally ill patients may be dependency, meaninglessness, hopelessness, being a burden on others, loss of social role, and feeling emotionally irrelevant. (124) Existential concerns and distress are common in nursing home patients at the EOL. (125) Little, however, is known about professional palliative care providers' existential concerns supporting patients at the EOL. (126, 127)

The existential perspective has been explored by existentialist philosophers like Søren Kierkegaard, Victor Frankl, Jean Paul Sartre, Martin Heidegger, and in psychiatry famously by Irvin Yalom. David W. Kissane, a psychiatrist and palliative care researcher, is best known for his model of family therapy in palliative care, (128) and his work on demoralization. (129) Building on the work of Yalom (130), Kissane suggests eight types of existential challenges for patients with advanced illness: 1) death anxiety, 2) loss and change, 3) freedom with choice, 4) dignity of the self, 5) fundamental aloneness, 6) altered quality of relationships, 7) meaning, and 8) mystery. (131) To each of these, he offers a suggestion to doctors on how to facilitate adaptive responses.

Kissane suggests his typology of existential suffering to aid its recognition and management in patients. In this thesis, I show how Kissane's typology of existential suffering might also be useful in order to understand the challenges of doctors and other staff working in EOL care. However, the doctor's professional role is defined as a contrast to the patient role, thereby potentially also alienating itself from the vulnerability of its counterpart. Such an opposition may have consequences for the experiences and expressions of existential distress in doctors, their adaptive responses and facilitation strategies.

Arne Johan Vetlesen is a Norwegian philosopher of ethics and social philosophy. Vetlesen's existential approach to the clinical encounter opens for potential strengths of the doctor's own vulnerability to existential suffering. Acknowledging vulnerability as a basic element of humanity common to both patient and doctor, he argues, is a precondition for accessing the patient's perspective. (132) Instead of simply being a weakness, the doctor's vulnerability may be valuable to successful patient communication, as has also been shown in general practice. (133) Doctors' own existential vulnerability facing matters of life and death has been underestimated, (134) and it is unclear how such vulnerability should be viewed as part of a professional identity. These issues are explored in the context of the nursing home doctor's work in EOL care in paper III of this thesis.

2. Aims

The overarching aim of this thesis is to elucidate the doctor's role in end-of-life care in nursing homes, with a particular focus on drug prescriptions and the impact of existential vulnerability. The three studies conducted for its purpose had the following specific aims:

I. To describe what drugs doctors prescribe to and discontinue for patients near the end of life in three Norwegian nursing homes, and identify predictors of a clearly defined palliative drug therapy in the last days of life.

II. To systematically review and assess the published literature on the effectiveness and safety of drug therapy for distress relief in the last days of life of adult patients.

III. To explore the experiences of doctors working with dying nursing home patients and their families, focusing on the existential vulnerability of the doctors.

3.   Methods

This thesis is based on three studies with three different designs; two empirical studies and a systematic literature review. Paper I was a historical cohort study, Paper II was a systematic literature review, and Paper III was a focus group study.

3.1   Paper I – Cohort study

To investigate drug treatment for nursing home patients in the last few days of life, we collected drug prescriptions and other routinely registered data from the electronic patient records (EPRs).

Study population and data collection

We selected three urban nursing homes in Bergen on the basis of using an EPR system (GBD) optimized for data extraction, designed with research and quality improvement in mind, most importantly by having structured data input. (135) GBD was introduced in one nursing home in 2007, and not until later in all three included nursing homes. The system is from 2016 distributed to all nursing homes in Bergen. We had a close dialogue with the GBD software developer to ensure appropriate extraction of data. We also cooperated with representatives from the municipal IT department, who provided administrative data on admission and death dates from a separate data source. These were the only data not collected from GBD. Many variables were available for extraction from GBD, and for these I had to assess their relevance to our study aim, data completeness, and roughly assess the face validity and reliability of clinical data before deciding whether extraction and further analysis were worthwhile.

We included all 524 patients admitted from January 2008 and deceased before February 2013, and collected demographical data (age, gender, date of nursing home admission and death, long- or short term stay); diagnoses (ICD-10);(136) and medications (generic name, Anatomical Therapeutic Chemical (ATC) code,(137) drug formulation, regular or as-needed schedule, indication, dates of initiation, alteration or discontinuation). We cross-checked dates of admission, discharge and death with data

from the patient administrative system. Given medication was, at the time of the study, still documented on paper, and was not collected as it would have been considerably more time-consuming to collect and prepare for analysis.

Definition of palliative end of life versus curative/preventive drug therapy

Drug prescriptions were analyzed from the perspective of assumed palliative versus curative/preventive purpose in the dying population. This was approximated on the basis of indication, drug, and formulation as outlined in Table 1. The patient in this phase will at some point be unable to take oral medications, and require a parenteral alternative. Since the patient's condition and symptomatic relief needs may change abruptly, the patient will also require pro re nata (PRN) / as-needed / anticipatory prescriptions. However, both regular and as-needed prescriptions may be palliative in intention, and therefore we did not restrict the definition to as-needed prescriptions. All included nursing homes used the care pathway for dying patients formerly known as Liverpool Care Pathway, which is why this was included as a key word for dying in the prescription indication text.

Table 1. Definition of drug therapy

Palliative EOL drug therapy	Curative/preventive drug therapy
1) Any drug prescription with an explicit EOL care indication key word was included: palliative, terminal, death, death rattle, Liverpool Care Pathway, or EOL 2) Any prescriptions of specifically recommended injectable palliative EOL drugs for use in Norwegian nursing homes, (138, 139) regardless of missing EOL key words in the indication text	Any medication for regular use without an explicit EOL care indication.

Statistical analyses

User rates were established for drugs according to the above categories. Predictors of palliative EOL drug therapy were explored by χ^2-test, and subsequently by binary logistic regression analysis; dependent variable: palliative EOL drug therapy; independent variables: age, gender, length of stay, nursing home, diagnosis of cancer. All variables except age were analyzed as categorical. Significance was determined at a level of 5%. IBM SPSS Statistics 20 (SPSS Inc., Chicago, Ill., USA) was used for statistical analyses.

3.2   Paper II – Systematic literature review

To investigate the evidence for the effectiveness and safety of palliative drug therapy in the last days of life, we performed a systematic literature review. We registered the study in the PROSPERO database of systematic reviews prior to start, (140) (CRD42016029236) to avoid overlapping reviews and reduce the opportunity for selective reporting deviating from the planned protocol, known as reporting bias. Here, no other similar systematic review was documented. I came across an appendix to a draft version of the NICE guidelines of the care of dying adults with search strategy in July 2015, from which we adapted the search string to identify the dying population. The first date of literature search in our review was in November 2015, a month before the NICE guidelines were finally published. At this point the research group did not suspect that the NICE guidelines would include similar systematic reviews. We reported the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (141)

Search strategy, study selection and data extraction

With the assistance of a university librarian we searched the following databases (final search date December 21st 2016): PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, ClinicalTrials.gov, and SveMed+. We also hand-searched the reference lists of all included articles and relevant literature reviews. After removal of all duplicates,

studies were evaluated in a stepwise procedure for inclusion in the review (Figure 1), based on the inclusion criteria (Table 2).

Table 2. Inclusion/exclusion criteria and outcomes of interest (PICOS)

P - population	Adults (≥18 years) in their last two weeks of life or clinically considered dying, in any clinical setting and diagnosis
I - interventions	Palliative drug therapy
C - comparators	Any, where available
O - outcomes	Primary: symptom or symptom control measures regarding pain, breathlessness, anxiety, and nausea; number or degree of adverse effects; and mortality or survival. Secondary: level of consciousness, functional level, quality of life, and quality of care.
S – study designs	Experimental or quasi-experimental designs (clinical trial, cohort, or case-control)

Two authors (Kristian Jansen and Lisa Pont) performed title and abstract screening. Full-text assessments and data extraction were done in author pairs. We extracted data on the 12 articles finally included using the McMaster Critical Review Form for quantitative studies, (142) adding information on health care setting, time before death studied, diagnostic category, drug category, and drug administration route.

Quality assessment

We assessed the quality of the 12 finally included studies in author pairs, using the Effective Public Health Practice Project (EPHPP) Quality assessment tool for quantitative studies, (143) chosen for its applicability across various quantitative study designs. Studies were rated weak, moderate or strong on the following six components: selection bias, study design, confounders, blinding, data collection, and withdrawal. This gave a global rating for each study as follows: weak (two or more component weak ratings), moderate (one weak rating), or strong (no weak ratings).

Figure 1. PRISMA flow diagram of study selection
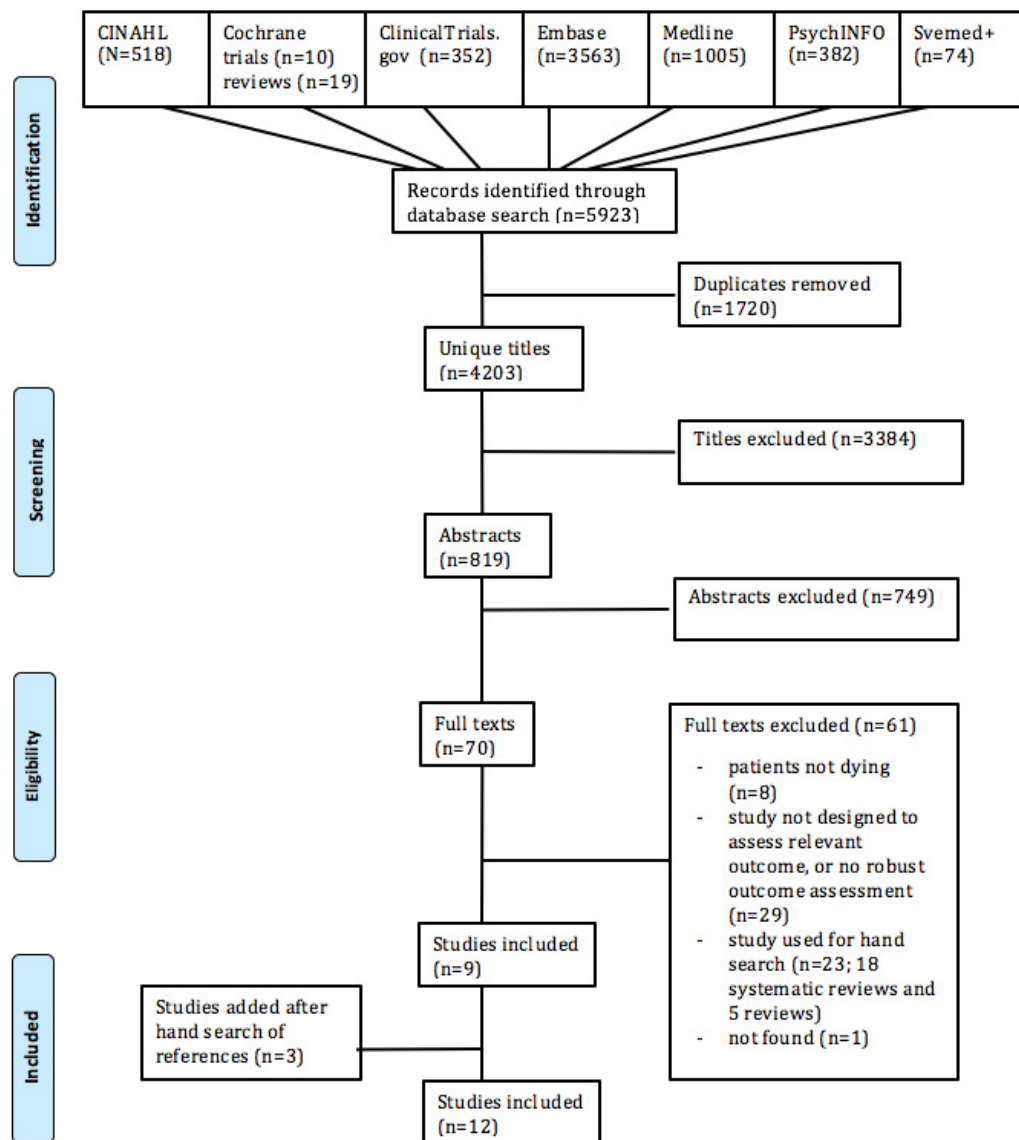
3.3   Paper III – Focus group study

To study the experiences of doctors working with dying nursing home patients and their families, we used focus group interviews. This design is suited to explore shared experiences in groups of participants. (144, 145) We conducted three focus group interviews, each including five to six nursing home doctors, from two Norwegian municipalities.

Recruitment

I recruited participants to the first focus group directly by email to the nursing home doctors, after having received the contact information from senior consultants in the municipality. In further recruitment this approach did not prove fruitful, and instead I approached local groups of nursing home doctors meeting for Continuing Medical Education purposes.

Participants

Participants were a purposive sample of 17 nursing home doctors, aiming for variation in gender (10 women, 7 men), age (33 - 65 years), clinical experience (3 - 29 years), part-time or full-time engagement (14 versus 3), and clinical specialty background (3 doctors were specialists in general practice, 3 hospital specialists, the remainder had no specialty background). I knew several participants in the first and second focus groups from earlier work as a nursing home doctor in the same municipality.

Interviews

In all three focus groups, I served as moderator while the last author served as secretary. To start off the conversation, in the first interview we asked participants to share a story of a dying nursing home patient that they had found particularly challenging. After the first interview, in an attempt to facilitate stories of vulnerability or challenges while also allowing for stories of success, participants were instead invited to share an experience that had made a profound impression on them. A brief interview guide was used (Table 3). Interviews lasted 90 minutes, and were taped and transcribed verbatim.

Table 3. Brief interview guide.

Point of departure:

Now I would like for us all to do the following exercise, of holding in our minds the image, story or situation of, a dying patient that made a profound impression on us, be it in a good way or a bad way. Take a moment to do this. As we speak together now, try to return to this patient. Could you please share your experience? How was it like?

Auxiliary questions:

- How did you experience the assessment of prognostication in the dying? Who was the first to understand that the patient is dying, and who was the first to point it out? How was it communicated? What clues do you use to assess the patient as dying?

- How were patient, family, staff and you yourself prepared for the death of the patient?

- How does treatment of dying patients differ, if at all, between diagnostic groups (dementia, cancer, heart failure)?

- What did you find particularly challenging? What made it so?

Analysis

All authors participated in the analytical process following the steps according to Systematic Text Condensation (Fig. 2). (146) First, we read the transcripts for an overall impression, identifying preliminary themes. Second, all authors independently identified units of meaning and coded these, representing different aspects of challenging experiences in EOL care and how these were dealt with. Third, we abstracted the content of the code groups and subgroups into condensates, each illustrated by a quotation. Fourth, we developed generalized descriptions of experiences with dying patients associated with existential vulnerability in an iterative process. In reaching the final categories, theoretical perspectives from Kissane's

exposition of existential challenges for patients with advanced illness (131) and
Vetlesen's emphasis on the vulnerability of the doctor (132, 147) assisted the
interpretation and focus on existential vulnerability.

Figure 2. Analytic process – systematic text condensation (Modified with permission
from: Malterud K. Kvalitative metoder i medisinsk forskning. [Qualitative methods in
medical research] 3rd ed. Oslo: Universitetsforlaget; 2011. (148)
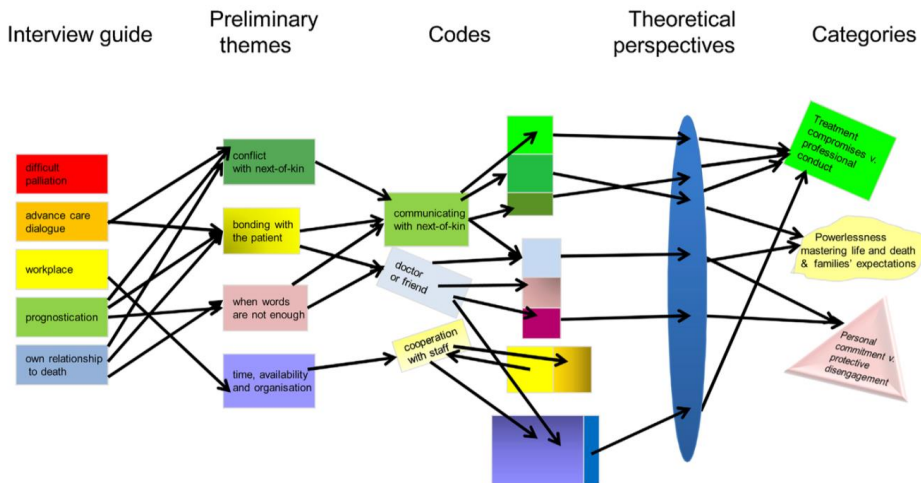
3.4   Ethics and approval

Paper I: We met with representatives from the municipality of Bergen as well as the
directors of the three included municipal nursing homes before data collection,
achieving approval for participation in the project.

The Western Regional Committee for Medical and Health Research Ethics (REC west)
(2012/1748) and the Norwegian Social Science Data Services (NSD) (#30691)
approved the study. To secure confidentiality, an external IT consultant performed
data extraction, replacing ID-numbers with a running number, the key to which
remained undisclosed to the research group.

Paper II: This study did not gather sensitive or personally identifiable data and therefore did not require approval from the instances mentioned above.

Paper III: REC west (2012/1091) and NSD (#31098) approved the study. Written informed consent was obtained from study participants, and pseudonym participant names were used in the transcription and analysis.

4.   Results

4.1   Paper I - Jansen K, Schaufel MA, Ruths S. Drug treatment at the end of life: an epidemiologic study in nursing homes. Scand J Prim Health Care 2014;32:187-92.

Drug prescriptions of 524 deceased nursing home patients were examined, focusing on palliative versus curative/preventive drug prescriptions in the last days of life.

Median (range) age of population at death was 86 (19–104) years, 59% were women. On the day of death, 99.4% of the study population had active prescriptions; 74.2% of palliative drugs either alone (26.9%) or together with curative/preventive drugs (47.3%). The most common palliative drugs were morphine (71.4% of patients), midazolam (55.0%), glycopyrronium (46.9%), and haloperidol (46.9%). Palliative drugs were associated with nursing home, length of stay > 16 months (AOR 2.10, 95% CI 1.12–3.94), age (1.03, 1.005–1.05), and a diagnosis of cancer (2.12, 1.19–3.76). Most initiations of palliative drugs and withdrawals of curative/preventive drugs took place on the day of death (Figure 3).

Figure 3. Patients (%) with at least one prescription changed in the last 14 days of life
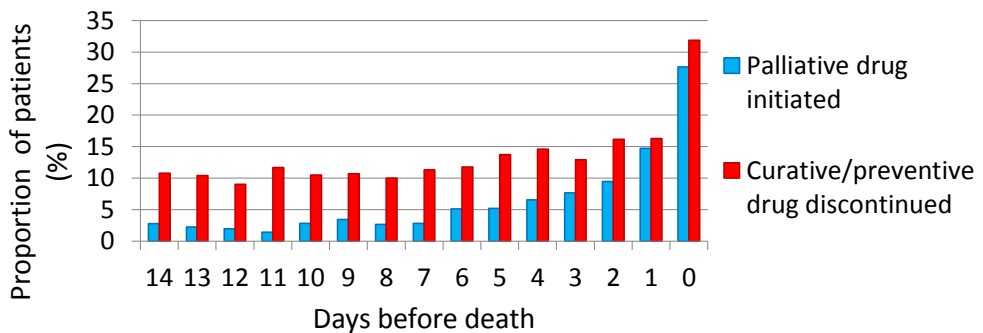
We conclude that palliative drug therapy and drug therapy changes are common for nursing home patients on the last day of life. Frequent last day changes may point to prognostication difficulties.

4.2   Paper II – Jansen K, Haugen DF, Pont L, Ruths S. Safety and effectiveness of palliative drug treatment in the last days of life - a systematic literature review. Accepted for publication in J Pain Symptom Manage.

This systematic review assessed the evidence base of palliative drug treatment in the last days of life based on a literature search of seven publication databases.

Of 5940 unique titles identified, 12 studies met the inclusion criteria (Figure 1). Heterogeneity of studies prevented meta-analysis. Seven studies were set in palliative care hospital units or hospices; with one of these also including home care patients. The remaining four studies were set at non-palliative care hospital wards. All studies were either exclusively or predominantly conducted in patients with a main diagnosis of cancer. Data was found for all primary outcomes (symptom control, adverse effects, survival), but only for the secondary outcome of level of consciousness.

Five studies (four RCTs, two of them placebo controlled, and one prospective cohort study) assessed anticholinergics for death rattle, providing no evidence that scopolamine hydrobromide and atropine were superior to placebo. Five studies (two RCTs, three prospective cohort studies) examined drugs for dyspnea, anxiety, or terminal restlessness, providing some evidence supporting the use of morphine and midazolam. Two studies (one RCT, one retrospective cohort study) examined opioids for pain, providing some support for morphine, diamorphine and fentanyl. Eight studies included safety outcomes, revealing no important differences in adverse effects between the interventions, and no evidence for midazolam shortening survival. Overall, included studies were small scale and only two were considered to be of strong quality.

We conclude that there is a lack of evidence concerning the effectiveness and safety of palliative drug treatment in dying patients, limiting guidance for clinicians on how to assist pharmacologically in a distinct and significant phase of life.

4.3 Paper III - Jansen K, Ruths S, Malterud K, Schaufel MA. The impact of existential vulnerability for nursing home doctors in end-of-life care: A focus group study. Patient Educ Couns 2016;99:2043-8.

This qualitative study explored the experiences of nursing home doctors through three focus group interviews, focusing on the impact of their existential vulnerability.

We found that nursing home doctors experienced making difficult treatment compromises in order to assist patients' and families' preparation for death, balancing these with their sense of professional conduct. They described lengthy negotiations and grief work processes demanding both patience and consideration, before they saw families reaching an acceptance of the futility of further interventions such as tube-feeding or intravenous drips.

Existential vulnerability also manifested as powerlessness mastering issues of life and death and families' expectations. The doctors could fall short of consoling, of upholding assurances to patient or family, and described uncertainty responding to inquiries of prognosis. Even in cases where death was clearly imminent, the doctor could feel guilty of being the «bad informer» revealing the prognosis.

Nursing home doctors balanced personal commitment with protective disengagement on the patient's deathbed. They described hesitancy engaging in conversations about death, and the need for a professional distance to the patient, that could lead to guilt. On the other hand, doctors' time spent by the deathbed, either hearing patient stories, comforting with words, or daring to be informal with the patient could trigger a deep sense of satisfaction as well as improve professional coping.

We conclude that existential vulnerability is experienced as a burden in the form of powerlessness and guilt in difficult treatment compromises, and a need for protective disengagement; but on the other hand also as a resource, in communication and in professional coping.

5.   Discussion

This thesis is based on three papers with different study designs. Selected methodological considerations are therefore discussed separately for the three papers in section 5.1, with ethical considerations finally considered jointly at the end of this section. Results are discussed in section 5.2.

5.1   Methodological considerations

Paper I was a historical cohort study investigating drug prescriptions to nursing home patients in their last days of life, Paper II was a systematic literature review assessing the evidence base for palliative drug treatment in the actively dying, and Paper III was a focus group study exploring the experiences of nursing home doctors, focusing on the impact of existential vulnerability.

5.1.1 Paper I

Design

The historic cohort design was suitable for the descriptive and exploratory purposes we aimed for, and a realistic study design within the resource constraints of time and funding. It also avoids the effect that study participation may have on human behavior in a prospective study, (Hawthorne effect) i.e. the nursing home doctors' prescribing behavior. On the other hand, the retrospective design is generally more vulnerable to confounding and bias than prospective designs.

Data reliability and internal validity

Reliability refers to the repeatability of findings, while validity refers to the credibility and applicability of the research. Internal validity asks whether the study credibly investigates what it is meant to, whereas external validity asks in what contexts the findings can be applied.

Dates. Admission, discharge and death dates were cross-checked with data from patient administrative records, confirming good validity for these variables.

Medications. A complete set of recorded medication data of all deceased patients during their last stay was collected, including both regular and as-needed medications. This limits the selection bias of medication data in the study nursing homes. Prescribed medication may overestimate figures if they are interpreted as drug use, but more adequately reflect the doctor's treatment decisions than given medication, particularly for as-needed medication. This is appropriate to the overall aim of the thesis of understanding the doctor's role in EOL care in nursing homes. There may be a delay between when the drug change is decided and when it is documented in the EPR. Such a delay could lead to underestimation of discontinuation of curative drugs and prescription of palliative drugs near death in this study.

Indication text had a high degree of completeness, present in 99.6% of all drug prescriptions on the day of death. Although drug indications are not standardized in nursing homes, the free text of indications is probably representative for everyday nursing home practice (pragmatic validity).

Diagnostic information. All patients had at least one diagnosis registered in their EPR. The degree of completeness and validity for these data is unknown, but some observations do raise questions. For example, the 36.8% prevalence of dementia in our deceased study population was considerably lower than the 84.3% found in cross-sectional assessment of Norwegian nursing home patients (11). This could point to under-diagnosis of dementia in our population. Another explanation could be that the prevalence of dementia in patients dying in nursing homes is considerably lower than that of the general nursing home population. Patients with a diagnosis of dementia had significantly longer duration of stay, meaning more patients without dementia died after shorter stays, and a higher turnover of patients without dementia. When only the deceased patients are counted the prevalence of dementia of the nursing home population may therefore be lower compared to a cross-section of the nursing home population. Underestimation of dementia could also occur if patients with dementia more often than those without dementia die elsewhere, most likely a hospital. I have not found figures from Norway regarding this, but this is from experience unlikely. We attempted validating the diagnoses of dementia with cognitive test scores (Mini-

Mental State), but these were not sufficiently complete in the EPR to be used. The study started in the early years of EPR use in nursing homes, when both medication data and clinical data were gradually starting to be put in electronic form. This may have challenged data completeness.

Definition of palliative EOL versus curative/preventive drug therapy

As there is no standardized definition of what constitutes palliative drug therapy in the last days of life, such a definition had to be made by the research group, using both indication text and drug class/drug formulation (Table 1, Methods).

The inclusion of specifically recommended (29, 138) palliative EOL drugs ensured that palliative prescriptions were not missed regardless of missing EOL key words in the indication text. In nursing homes, injectable antipsychotics and benzodiazepines may on occasion be used to treat neuropsychiatric symptoms of dementia. We found a median of two days from prescription to death for these two drug categories, making it likely that these prescriptions were issued for their palliative indications. While anticholinergics have several indications, including urinary incontinence, glycopyrronium and scopolamine in injectable form are seldom used for non-palliative purposes in nursing homes. Restricting the palliative prescriptions to injectables, we excluded prescriptions less specific to the dying patient, such as tablets, oral suspensions and patches.

Out of 1306 palliative EOL prescriptions in our study, 1276 (97.7%) were identified by the drug class criterion alone, while 585 (44.8%) were identified by the indication text criterion alone. The drug class criterion was therefore the most decisive criterion in the definition of drugs relevant to the dying phase, but the joint definition of both criteria further increased sensitivity.

As-needed prescriptions with no explicit palliative purpose and injectable formulation (21.3% of all prescriptions on the day of death) were intentionally excluded. The bulk of these prescriptions concerned oral medications such as laxatives or oral diuretics, most likely unsuited for a dying patient normally lacking the ability to take oral medications. As for the purposes of our main analytical categories of palliative versus

curative/preventive, I find this choice appropriate also in retrospect, although possibly introducing some misclassification bias.

A strict dichotomy of curative/preventive versus palliative intention does not adequately reflect clinical practice, where drug therapy may serve both or unclear purposes, for example in the case of diuretic treatment of congestive heart failure, or in treating pneumonia with antibiotics for its exacerbation of dyspnea, delirium, or pain. In a Dutch study, 8 % of antibiotic prescriptions to nursing home pneumonia patients with dementia were given with a palliative intent. (149) Indication text key words would likely identify the palliative intention of such prescriptions, but perhaps not all.

External validity

Sample size was relatively large with 524 consecutive patients included, limiting selection bias. Due to the exploratory nature of this study, no power analysis was performed. A limitation of patient and nursing home sample size lay in restricting the study to a convenience sample of nursing homes using a particular EPR only used in a few nursing homes in Bergen at the time – "Geriatrisk Basis Datasett" (GBD). (150) Generalizability of our study is extended by the fact that the study population comprised patients from different types of wards. On the other hand, since nursing home was a predictor of palliative drug treatment in our results, and prescription patterns are known to differ across nursing homes, (100) the small number (N=3) of participating nursing homes could contribute to selection bias. International interpretation of results must also have in mind the characteristics and role of Norwegian nursing homes in health care mentioned in the background chapter of this thesis. There is possible comparability with countries with similar relative national health expenditures on LTC facilities, such as the Netherlands, Switzerland, Belgium, Denmark, and Sweden. Differences in people (patients and staff), organization, tools and technology, tasks, and environment are also known to play a role in drug treatment in nursing homes. (151) Despite organizational differences, similar barriers and strategies in EOL care for nursing home doctors have been shown between Norway and the Netherlands. (17)

5.1.2 Paper II

Comparison with the systematic reviews in the NICE guidelines

This systematic review addressed the prevalent and relevant issue of distress in the dying, and its pharmacological relief. It is comprehensive, including seven different databases, and employing broader inclusion criteria than has previously been done. Specifically, compared to the reviews on which the 2015 NICE guideline are based (30), paper II includes cohort design studies in addition to clinical trials and case-control studies, and articles in seven languages in addition to English. While this sets the inclusion criteria bar for study design lower on the quantitative evidence-hierarchy, (152) affecting the strength of recommendation that may result from the review, it may be more sensitive in identifying studies that could contribute to the body of evidence.

The number of systematic reviews in medical research is increasing, yet not keeping up with trials. (153) While our systematic review overlaps with some of the reviews in the NICE document, such overlap may serve important purposes. (154) For one, the eligibility process of included studies has clearly resulted in somewhat different studies included. Second, findings from systematic reviews can also benefit from replication. On comparison, I discovered what seem to be an error in the reporting of results in one of the NICE guideline reviews, as well as in a Cochrane review, which although concerns a result, I will mention here as an illustration of the importance of repeating systematic reviews. In the NICE guidelines, (30) a clinical benefit of the morphine plus midazolam combination compared to either drug alone for dyspnea is reported after both 24 and 48 hours compared to both drugs, while the study in fact reports no significant difference compared to morphine alone after 48 hours, but is indeed significantly better compared to midazolam alone, in terms of proportion of patients with uncontrolled dyspnea. The lack of difference for the morphine group after 48 hours is correctly presented in the table, but the text concludes that the effect is simply less pronounced after 48 hours. This may be a case of different interpretation of the results compared to paper II. However, a Cochrane review (155) to the contrary reports "without any difference when comparing the three arms after 48 hours". This is in my opinion also an inaccuracy, although the lack of difference in dyspnea intensity

between groups supports a lack of difference in effect. Whether we regard these differences as inaccuracies or different interpretations between reviews, they seem not to have affected the main conclusions of neither the NICE nor the Cochrane reviews.

Eligibility evaluation of full-text papers requires a template for data extraction, in order to understand their content, assess their quality, and report their results. We employed rigorous data extraction (McMaster critical review form) and quality assessment procedures (EPHPP). The EPHPP, although it grades the quality of individual studies, does not quantify the overall evidence across studies, nor does it grade strength of recommendations, nor is it easily applicable to individual outcomes. Quality of evidence across studies can be systematically graded based on a hierarchical assessment of study designs included in the body of evidence supporting a given association or recommendation. There are several options available to rate quality of evidence. (152) The GRADE system, (156) widely-adopted and used in the reviews of the NICE guidelines, is the only that considers strength of recommendation separate from quality of evidence. However, our study did not aim to develop guidelines, a process demanding far more than an overview of the evidence, and a task for larger research-, clinical-, and policy-making cooperatives to reach consensus on. The EPHPP quality assessment is more straightforward and was therefore deemed suitable to our ambition and purpose.

5.1.3 Paper III

Three central measures in the reporting and evaluation of qualitative studies are the notions of relevance, validity, and reflexivity. (157, 158) While relevance is addressed both in the background and in the discussion of results, validity and reflexivity will be addressed here.

Reflexivity and preconceptions

Reflexivity is defined as "An attitude of attending systematically to the context of knowledge construction, especially to the effect of the researcher, at every step of the research process". (157) Reflexivity is a frame of reference in which to approach discussions particularly related to limitations and strengths of the study, and the

transferability of findings. I have therefore attempted to demonstrate reflexivity in all sections of the methodological considerations with respect to paper III. In this section, however, I focus on the role of my preconceptions, and the impact of my own experiences on developing the research question, analysis and interpretation of the study.

For paper III, I initially set out to explore the challenges of the nursing home doctors in EOL care work, with a presupposition that difficulties abound in this work; that in exploring these difficulties, they may be better understood; and that sharing this understanding would be helpful to nursing home doctors and their dying patients. Paper I added to suspicions that prognostication of death might be a central difficulty. My own experiences of difficult yet sometimes profoundly touching encounters with dying patients and their families in crises have, since I started working in nursing homes in 2007, both challenged and rewarded me both on a personal and professional level. I may therefore have had a special awareness for aspects of EOL care that are personally and professionally challenging yet rewarding.

On seeing glimpses of vulnerability in the stories of doctors interviewed in the first interview, I realized that the research question was perhaps not best attacked directly by asking for "challenges", even though I may have been looking for these initially. As was pointed out to me by fellow researchers, limiting the research question to "challenges" may simply have been an expression of my own preconceptions. Asking for "experiences" both provided an indirect and perhaps less intimidating opening even when looking for challenges, and importantly, opened for the observation that "challenges" may not be neither the most relevant nor most common descriptor for doctors' experiences.

As a central aid to reflexivity throughout the research process, and supporting analysis as well as my own learning, a decision trail was used. (159) This document included all email correspondence, supervision minutes, and developments to the study from conception to publication.

Recruitment and participants

Recruitment was purposive, selecting participants with the aim of diversity with respect to age, gender, working experience, and nursing home institutions. The line between purposive and convenience sampling may be unclear, however. As an example of difficult recruitment in paper III, an attempt to organize a focus group with doctors from rural nursing homes in northern Norway was unsuccessful. In the last interview, all participants belonged to a fixed group meeting for continuing education (CME) purposes, and no changes to the groups was attempted made, as its composition was deemed satisfactory. The second focus group was a combination of a CME group and other participants, while the first group was composed entirely by individual selection of participants. The concept of *information power* has been suggested as a more relevant factor than the number of participants and interviews for the ability of qualitative studies to contribute new knowledge. (160) The more information power in a study, the fewer participants are needed and vice versa. Information power is facilitated by the narrowness of aim, sample specificity, quality of dialogue, by whether established theory is applied and single-case (versus cross-case) analysis is aimed for. Information power in paper III was thus facilitated by a narrow aim of addressing existential vulnerability, a specific sample of nursing home doctors with experience from working with dying patients, good quality dialogue, and the application of existential theoretical perspectives in analysis. Cross-case analysis of diverse experiences of several nursing home doctors in EOL care demanded more participants than would a case study. Overall, and in light of these aspects of information power, I judge sample size to have been appropriate.

Analysis

Systematic text condensation (STC) has been developed by Kirsti Malterud, a researcher and colleague at the Research Unit for General Practice in Bergen. This method for qualitative text analysis has been clearly and didactically described. (146) Other qualitative analytic methods apt for descriptive thematic text analysis could have been used such as Grounded Theory, (161), Template analysis (162), or Interpretative

Phenomenological Analysis (163). Methods of longitudinal analysis such as Narrative analysis could have also been employed, as data was rich in terms of stories.

STC is inspired by Giorgi's psychological phenomenological analysis and, as most qualitative methods, is founded on phenomenological philosophy. It is however intended more as a procedure than a theoretically dedicated method. (146) STC therefore grants researchers much flexibility with respect to the theoretical perspective to be applied upon the research question, and even to refrain from applying one. Theoretical frameworks may be applied in different manners and at different stages in the analytic process. (164) In paper III, the decision to apply a theoretical framework was made toward the final stages of analysis, where we felt the need to sharpen analysis with respect to emerging vulnerability issues. Theory in paper III was chosen based on the interests and acquaintances of the first and last authors with existential perspectives in philosophy and psychology. In particular, my co-supervisor and main qualitative supervisor Margrethe Schaufel had done previous research on how existential challenges affect doctor-patient-interactions and decision-making processes at the cardiology ward. In her thesis, she applied the existential philosophical perspectives of the Norwegian philosopher Arne J Vetlesen. I became familiar with the work of the oncologist David W Kissane through exploring research literature on existential distress in palliative care. Kissane builds upon the work of existential psychiatrist Irvin Yalom, whose work I was also acquainted with.

Naturally, other theoretical perspectives were discussed, such as Shared Decision-Making, (165) and would have taken analysis in different directions, underscoring the active role of the authors in shaping the product of qualitative analysis.

Transferability

Transferability is synonymous with external validity, and concerns how the findings of the paper may be applied in other settings. (148) Although we believe international comparisons to our results are reasonable within a Western cultural setting, doctor's experiences are likely to be influenced by factors such as doctor availability and EOL

care competence, role of nursing home in health care, and cultural differences in attitudes toward death and dying, communication, and faith or worldview.

In particular, doctor availability and staff resources are likely to allow more time for patient and family dialogue, and the reflection and self-care that have been shown central to coping with the emotional, physical, and existential demands of EOL care. (116, 122, 126, 166) Although it is difficult to find comparable figures of doctor availability in LTC facilities internationally, as mentioned earlier, relative health expenditures in LTC facilities likely indicate differences also in this regard. (13)

The existential perspective is in a sense culturally inclusive, by taking as a starting point the most basic elements of the human existence conceivable, and shared vulnerabilities across humanity. This may make findings relevant to a wider audience, across cultural or religious background. Regardless of its inclusive aim, the philosophical/psychological language used in the existential tradition may also feel strange or unaccustomed to some, as it long did to me. Discussing issues surrounding death will likely often be difficult and special in spite of shared concepts and language. Kissane developed a typology for doctors to be able to recognize, talk about, and manage existential distress in patients. I have attempted to broaden the relevance of this typology by applying some of its ideas on the experiences of nursing home doctors working with dying patients.

5.1.4 Ethics

While this thesis ultimately aims to benefit the nursing home patient and their closest kin, it primarily addresses the efforts of the nursing doctor, central in the staff team working to this end. While this aim is easily justified, the contribution of research must also exceed the burden of its process. This first implies a number of considerations regarding participants and subjects in the research. There is fortunately no burden to patients in any of the studies.

The stories the focus group participants told were sometimes evidently difficult to share, revealing of shortcomings and weaknesses, and eliciting emotional reactions. Even so, the feedback received was positive and encouraging, and many participants

expressed a sense of meaningfulness of participating. Anonymity was ensured through pseudonym participant names, and secure storage of audio recordings and transcriptions, in a protocol approved by the regional ethics committee and the Norwegian Social Science Data Services. Recruitment was sought to be made as confidential as possible in the first focus group, where the group did not meet regularly for education purposes, as most participants did in the last two groups. I was acquainted with several of the participants in the first and second focus groups from previous work in the same municipality, and they may therefore have felt more of a pressure to participate when I asked them than if I had not known them. This may also have affected what these participants shared in the interviews, for example by a wish to please me.

5.2.   Discussion of results

5.2.1   The doctor's role in EOL care in nursing homes – a position of uncertainty

I will discuss below selected issues related to the results of the studies in this thesis. As a unifying perspective, I will demonstrate how the nursing home doctors' position in EOL care work is characterized by uncertainty in several distinct regards. I will address these in turn.

Uncertainty prognosticating death

Although this thesis does not specifically investigate prognostication, some findings point to uncertainty regarding prognostication, or rather, that death comes unexpected. In paper I we found a marked increase of drug therapy changes on the day of death. If medications are being continuously reviewed with respect to relevance, such as ideally is the case, then such a marked increase of drug changes points to death coming unexpectedly. Doctors interviewed in paper III also expressed uncertainty regarding recognizing the dying phase.

Survival prediction studies on home-dwelling or hospice patients with cancer dominate, for whom several models of prognostication have existed for years, based on function and performance scales, symptoms and clinical or laboratory

measures.(167-169) "Would I be surprised if this patient died in the next 12 months", sometimes called the "surprise question", has been recommended in the UK to identify patients at high risk of death who might benefit from palliative care services, (170) but performs poorly to modestly as a predictive tool for death, and worse in non-cancer illness. (171) Disease trajectories for non-cancer diseases such as dementia and organ failure, more prevalent than cancer in nursing homes, are harder to predict. (172-174) The eldest patients above 85 years of age have been underrepresented in prognostication studies, but measures of physical performance have been found to be predictors of survival also in this group. (175) Prognostic tools to estimate 6- and 12-month mortality in nursing homes have nevertheless been shown to perform fairly well. (176)

The role of professional background and experience in prognostic ability of death is uncertain. (177) In the last month of life, actual survival and clinical prediction by doctors are correlated, but doctors are systematically optimistic in their prognoses. (178-180) In a study from an inpatient palliative care unit (PCU) in Ireland, in a population of median actual survival of 20 days (range 1-635), no staff group placed patients in the correct survival category more than 50% of the time, nursing and junior medical staff being more accurate than senior doctors and nursing assistants. (181) The difference compared to senior doctors was attributed to more frequent assessment opportunities. This contradicts a previous study finding that prediction ability improved with doctor experience. (182)

On the brighter side, survival predictions become better toward the final days of life; (179) nursing home doctors have been shown to be accurate in more than 90% of their prognoses in the last seven days of life. (183)

Uncertainties related to non-cancer conditions and in particular dementia

As paper I also showed, being prescribed palliative drug therapy on the day of death was associated with a diagnosis of cancer. In other words, patients with non-cancer conditions may present an additional uncertainty to nursing home staff. Unpredictable illness trajectories of non-cancer illnesses such as chronic obstructive pulmonary

disease (COPD), heart failure, and dementia challenge not only prognostication, but also recognising and meeting the changing needs of pharmacological symptom relief, adding to uncertainty. (184, 185)

Advanced dementia is a terminal illness particularly prevalent in nursing home patients, challenging communication, symptom assessment, prognostication, autonomy and decision-making. (186-189) Dementia leads to uncertainty regarding treatment decisions, appropriate care setting, and care provider, and timing of palliative interventions. (190) Anticipatory prescribing of palliative drugs in acute geriatric wards has been shown to be less frequent in the last 48 hours of life of patients with frailty or dementia than in those with cancer. (191)

Dementia was the most common diagnosis of the deceased nursing home patients in paper I, but was not independently associated with palliative drug therapy (or the lack of). A negative association could have been expected, as dementia as mentioned poses particular challenges to proxy assessments in EOL care. Likewise, in all dying patients with reduced capacity to communicate, recognition of pain and other symptoms must be done with proxy assessments. The validity of proxy assessments can be questioned, but alternatives are hard to imagine. Communication difficulties associated with dementia are known to challenge decision making in the nursing home, (186) and may also have contributed to the late drug changes observed in paper I.

Diagnostic uncertainty in the nursing home setting

Nursing homes and the primary health care setting in general lack diagnostic resources compared to hospitals, such as diagnostic imaging, on-the-hour blood analyses, specialist second opinion, etc. The nursing home doctor hence works in a greater diagnostic uncertainty, which, if accepted, may spare the patient unnecessary relocations or invasive procedures, but also challenge treatment decisions. On the other hand, fewer doctors will be involved in the medical care provided in nursing homes and the primary health care setting compared to hospitals. This provides continuity of care, and may contribute to better knowledge of the patient, facilitating communication and therapeutic alliances.

Uncertainty regarding effectiveness and safety of drugs

Regarding knowledge on effectiveness and safety of palliative drug therapy, almost all studies included in paper II were conducted in the oncological or palliative care unit setting. This points to a particular lack of research-based knowledge on EOL care in the nursing home setting. (192)

Paper II reveals the marked lack of research evidence of effectiveness and safety of drug therapy in the dying. Specifically, we may not know which is the most effective and safe pain-relieving drug therapy option in the dying, and anticholinergics are probably not worthwhile for death rattle. Doctors must therefore base clinical practice on experience, and from research on other patient groups.

Not all distress of dying may be fully relieved. Staff may fail to recognize symptoms and complaints, fail to adequately treat them, or the symptoms are simply beyond remedy. In a Norwegian study, on the day of death, while the administration of opioids, midazolam, and anticholinergics increased and were associated with some symptom relief of pain, anxiety, and depression, most symptoms were still present after treatment, and moderate to severe dyspnea and death rattle increased. (27) In a Swedish study, while pain was the symptom with the highest proportion of symptoms relief, other less prevalent symptoms were also less well-relieved. (26) Poor symptom control at the EOL despite extensive drug treatment has also been found in US and Dutch nursing homes. (193-195) Doctors may attempt to treat intractable symptoms by sedation. (196, 197) To some, the inability to relieve suffering at the EOL is an argument for hastening death or euthanasia. (198) Doctors and other staff working with dying patients must therefore be prepared for the possibility that not all symptoms may be fully relieved.

On the other hand, treating physical symptoms alone may not be the main determinant for quality of dying in nursing home patients. In after-death interviews from LTC facilities in the US, pain and dyspnea were not associated with a poorer quality of dying as perceived by families of deceased residents, and could alert staff to the need for care. (199) Unfulfilled needs of doctor communication, emotional support, and

being treated with respect, (200) are hardly met by drug treatment. The EOL care experience has multiple domains apart from physical symptoms: quality of life, emotional and cognitive symptoms, functional status, ACP, continuity of care, spirituality, grief and bereavement, and caregiver well-being. (201)

If drug therapy does not work, and the doctor is stripped of a central tool and power, how does this impact the doctor's role in EOL care? We move on to the uncertainty expressed by doctors interviewed in paper III.

The doctor's uncertainty and existential distress working with dying patients

The certainty of death contrasts the uncertainties surrounding it. Contemplating the possibility of dying opens for a wide variety of concerns often termed existential distress. Such contemplation and distress is inextricably linked to being human, mortal, and in particular to facing life-threatening illness. As a general human vulnerability, existential distress is reasonable to expect also in staff working with the dying, although this has been less studied. (127)

Paper III shows how existential vulnerability, our common vulnerability facing threats to our existence, presents in the experiences of nursing home doctors working with dying patients. It presents as feelings of powerlessness, uncertainty and guilt facing prognostic and palliative challenges, in the difficult balance of treatment compromises with next-of-kin with professional conduct, and in the occasional need for protective disengagement from difficult situations. In the view of Kissane's existential typology, powerlessness may be enhanced by the doctors' own need for control, and the shared human anxiety for death, the stigma of death, and doctors' sense of responsibility may contribute to vulnerability.

5.2.2   End of life care strategies for nursing home doctors

In a situation characterized by the uncertainties discussed above, how should nursing home doctors cope? Based on the findings in the three studies comprised by this thesis, I propose four ideas to meet the mentioned uncertainties of EOL care work in nursing homes:

1. Research in EOL care and nursing homes

2. Integrated ACP and grief work dialogue with patient and family

3. Self-reflective practice

4. Adjusting interventional strategy, relational strategy and focus of self-awareness with deteriorating prognosis

1. Research in EOL care and nursing homes

When not reducing uncertainties, research may help us understand them better. Paper II confirmed a need for research in the palliative treatment of the dying. There is an abundance of methodological and structural challenges to conducting research in palliative care, providing some explanation for the small number of studies we found in our review. Close to death, high attrition rates in particular limits sample size in palliative care studies. (202) This was of consequence in several of the included studies in paper II (203-205).

Generally, central challenges exist in the domains of study design, assessment and classification of symptoms and signs, obtaining informed consent, recruitment and engaging stakeholders, ethical issues, funding, and policy issues. (206-210) Researchers also describe public and professional apprehensions concerning participant burden, misunderstandings of EOL care, and aversions to serious illness to be significant barriers. (202, 211) International collaboration is becoming increasingly important to address priorities in EOL care, and for funding bodies to share experiences from successful funding frameworks. (212) In heart failure palliative care research, as an example of one of the better studied non-cancer conditions, unpredictable illness trajectories challenge the identification of the dying phase, and therefore participant eligibility, user involvement, and contributes to participant attrition. (213)

Distinguishing between symptoms such as pain, anxiety, and restlessness in the actively dying is not easy, and neither is symptom assessment of patients with reduced ability to communicate, such as commonly in dying patients or patients with dementia.

Assessments for these patients rely on the ability of staff to interpret behaviours and signs such as restless movements, sounds or facial expressions. The proxy judgement of distress in these situations is vulnerable to misunderstanding (214-216). However, clinicians may not always need to distinguish between symptoms with overlapping presentation, since drugs often have multiple or sedative effects that may treat several of them. As examples in paper II, opioids or midazolam are used to treat both dyspnea, pain, and anxiety. Such overlap of both symptoms and pharmacological effects may make treatment strategies simpler, but complicate the design of RCTs, and research in general in this population.

The two trials studying respiratory tract secretions in the dying, known as death rattle, were placebo-controlled, (217, 218) a design presenting particular challenges in EOL care. Being an observable sign as opposed to a subjective symptom, the impact of death rattle on the patient may be questioned, and therefore the need for its pharmacological relief. A placebo-controlled trial may be unethical when a difference of effect between the "real" and the placebo intervention is clearly expected. For a clinical trial to be ethical there needs to be "equipoise" between the groups compared - an epistemic state of indifference. (219) If not, the placebo group greatly risks suffering harm, for example by having more untreated pain compared to an intervention group testing opioids for pain, making a study ethically unacceptable. (220) When the expected effect of the active intervention is more uncertain, the potential harm of a placebo group in comparison is also lesser, and equipoise between study treatment groups is greater. The use of placebo-control to study death rattle is perhaps therefore not as ethically controversial as in the case of the more subjective complaints, for which we did not find RCTs.

Importantly in palliative care, placebo effects depend on healing patient-therapist relationships and context of care. (221-223) These effects do not imply deception, as the placebo concept often is associated with, but may represent tangible benefits to patients. The skills and contexts conducive to them must therefore not be dismissed, but studied and cultivated. On the other hand, pharmacological treatments that add no benefit compared to the therapeutic relationship alone may not only be unethical but a

waste of resources. The studies by Heisler and Likar exemplify that a placebo control may be acceptable also in the dying population, as long as equipoise between comparison groups is respected. Crossover studies, where study subjects cross over between interventions compared during the study, or add-on studies, where subjects receive standard treatment plus the experimental treatment, can also make placebo controlled studies more ethically acceptable, but are difficult to perform in the dying population as observation time is limited. Nevertheless, one of the RCTs included in paper II, although not placebo-controlled, was in fact a crossover study. (205) The alternative to placebo control is an active control, which was used in the five other RCTs included. (204, 205, 224-226)

Challenges and proposed solutions to conducting research in nursing homes to a large extent mirror palliative care research challenges in general. For qualitative research, identified issues have been: informed consent, finding opportunities to conduct interviews, involvement of care home staff and residents' families, and maintaining privacy during interviews. (227) In addition, non-participation of nursing homes in EOL care research has been associated with the number of deficiencies (as listed in a public health department record) and a higher key staff turnover. (228) This last finding, if generalizable, confers an important risk of selection bias on nursing home research. Relating this to paper I, although the EPR used in the study nursing homes was used free of charge to the nursing homes in the study period, a selection of particularly resourceful nursing homes cannot be excluded.

The last two decades have seen a growth of research in EOL care in nursing homes. (229) Nevertheless, studies are few and mainly observational, and in need of relevant and validated measurement instruments for patient outcomes. (192) Trials of palliative care interventions assessing patient outcomes have been called for, particularly outside USA, (230) where organizational factors challenge comparison to other countries. (231, 232)

A number of strategies for dealing with the challenges of palliative care research in general have been suggested in the domains of study design, sampling, conceptual,

statistical, and measures and outcomes. (208, 209) Clinical trials in a palliative care population have shown not only to be feasible, but even to represent a positive experience for patients. (233, 234) Gysels suggests a model of research in palliative care, typified by participatory study designs, with tailored data collection from supported and supervised participants, and where immediate patient benefits are obtained in the form of empowerment, self-validation and an opportunity for altruism. Where objectifying and instrumental research is often framed in opposition to person-centered and empathic care, such a model allows for a culture that is open to research, and a research that is not in conflict with, but is embraced by the principles of care. (233)

To improve palliative care knowledge in nursing homes, creating a research culture in nursing homes and palliative care services, (235) and seeing the value of a range of study designs depending on the research question, including also qualitative designs and action research, has been proposed. (236)

2. Integrated ACP and grief work dialogue with patient and family

This thesis points to many changes to drug therapy in the last day of life of nursing home patients, indicating that death comes unexpectedly. Unexpected is relative. In nursing home LTC, where patients have a short remaining life-expectancy, death should in one sense not come as a surprise for any patient. It may instead be that the major impediment to preparing for the dying phase with appropriate changes to drug therapy is not the diagnostic ability itself, and the uncertainty of interpreting objective signs of dying in the last days of life. As mentioned, such prognostic ability has been demonstrated in the last days of life in the nursing home, and in several groups of staff. (183) A major impediment to "seeing" the dying stage may instead be the lack of communication with patient and family with respect to prognosis in good time before dying. In time before the dying phase, the staff should respond to uncertainty of prognosis by advance discussions of goals of care and treatment with the patient and/or family (ACP). Communication and treatment negotiations with family were central in the stories told by nursing home doctors in paper III.

ACP dialogue with patient and family potentially decreases the need for futile treatments. An example of likely futile treatment is raised in paper II, as the effect drug treatment of death rattle is not proven to be better than placebo, calling for non-pharmacological interventions such as information to family. Studies have shown a positive effect of early decision-making (ACP) on EOL care both in LTC and across settings of care, on patient and family satisfaction, reducing hospitalizations and costs, and improving concordance between patient's preferences and treatments received. (79, 237-240) Nursing home doctors also feel ACP discussions facilitate future decisions on medical treatment and EOL care. (117) While doctors have the formal responsibility for EOL decision making together with the patient and family, the nursing staff also need to be involved as discussion partners and sources of knowledge of the patient. (241) Patients lacking decision-making capacity are sadly lacking from ACP studies in nursing homes, (64) a large patient group in nursing homes. Doctors' concern for and judgement of these patients' best interest may come in conflict with next-of-kin's opinions, as shown in this thesis, and also in other interview studies from Norway. (63, 68) If all caregivers and staff are confident in honoring the patient's wishes, they may face death together with peace. A good ACP process, allowing for the doctor and staff to know the patient, mapping and settling the patient's care and treatment goals, may thus provide a counterweight to the uncertainties mentioned.

However, doctors interviewed in paper III described discussions not only for treatment decision-making, but also for preparing patients' and their families for the death of the patient. The task of preparing patients and their families or informal caregivers for death is sometimes called promoting "preparedness for death", or "pre-loss grief" work. The presence of pre-loss grief, and low preparedness for death appear to be risk factors for adverse bereavement outcomes such as complicated grief, and post-loss depression and anxiety, and interventions show a tendency for increased caregiving time to increase preparedness for death. (242) Preparedness is closely related to being "peacefully aware" of the terminal nature of illness, (243) and Kissane's "adaptive adjustment" to the existential distress of death anxiety. (131) While the concept of preparedness focuses on family and caregivers, cancer patients that are aware of their terminal illness and also feel "at peace", have lower rates of psychological distress and

higher rates of ACP, higher overall quality of death, and their surviving caregivers are healthier physically and mentally six months after their loss, compared to those who were not peacefully aware. (243) The fact that palliative drug treatment in paper I was associated with the longest duration of stay may support that increased caregiving time increases preparedness for death, and that getting to know patients and their families improves care. Dialogue with patient and family is likely to support a recognition of and appropriate response to the dying phase. Without an early-starting and continuous dialogue with patient and family, palliative changes to drug therapy may come unexpected to unprepared family, and demand more time-consuming communication efforts from the staff than when the prospect of dying, its course, care strategy, and feelings are shared and discussed in advance. Restraints of time may then impede choosing a palliative strategy.

The dialogue with patient and family described by the nursing home doctors interviewed in paper III, integrated decision-making and grief work, and was described as a continuous and sometimes arduous process. A process perspective may be useful. Oncologists who view EOL care communication with dying patients as a process addressing patient and family acceptance of dying report increased job satisfaction. (244) A palliative response still requires that the doctor have knowledge of life expectancy considering the patient's health condition, as well as knowledge of time-to-benefit for all therapies. (43) A bedside doctor's assessment ensures a cross-disciplinary acknowledgement of the dying phase, and contributes to appropriate prescribing, but is difficult to achieve out-of-hours in nursing homes. Based on this, increasing doctor availability may have the potential to improve the early pharmacological response to the distress relief needs of dying patients in the nursing home.

What does a palliative strategy, and an early palliative response in drug therapy concretely mean in the nursing home in terms of drug changes? It cannot mean that all patients are to be prescribed parenteral morphine as needed, as this would likely increase inappropriate use. Symptomatic as-needed prescriptions must be reserved for the events of deterioration in condition, but with a low threshold for prescription. It

cannot mean either that all curative/preventive medications should be discontinued the moment you are admitted to LTC, as some of these will be appropriate. However, from the moment of admission, drug therapy must be reconsidered in the view of limited life-expectancy, and ACP dialogue must be started with patient and family. Doctors cannot postpone it until the dying phase is certain to prepare their patients and their patient's families for it. But as I will discuss next, doctors must also prepare themselves.

3. Self-reflective practice

The task of preparing for death is also relevant to health care professionals working with dying patients. Working in EOL care, health care professionals must endure the cumulative loss of many patients, some relationships, stories or encounters having profound emotional impact, making lasting impressions. (134, 245) Such stories and impressions were explored in the interviews with nursing home doctors in paper III. Health care professionals working in EOL care risk burnout, compassion fatigue, and poor quality of care, to which existential distress has been linked as a key contributor (126, 246).

The need for a professional distance from death and dying was described by doctors in paper III. In view of Kissane's existential perspectives, such need for distancing from death and dying is an expression of human beings' anxiety of death. Fear and uncertainty before death, subtle or ignored as it may be, is at the core of existential vulnerability. Mortality *is* the ultimate vulnerability. The American psychiatrist Irvin D. Yalom has been central in the development of a whole field of psychology called Existential psychotherapy, identifying existential concerns surrounding death, freedom, isolation and meaninglessness as primary sources of all major psychological defense mechanisms. (130) Fear of death is thus potentially a powerful force affecting our own emotions, behaviour and thinking, as well as our relationships with others. It has the potential to compromise patient care. (126) Death rattle is potentially an example – likely a false alarm for patient distress, but a concrete reminder of the proximity of death, and perhaps therefore, difficult to endure for family and staff. (247, 248)

Avoiding seeing death and clinging to cure is an escape not only for the patient or family, but also for the doctor and staff. In order to "see" death, we must bare to see it. To acknowledge that death is irreversibly coming, we must accept that even our most heroic curative efforts to prolong life, are not enough; that our most well-intended palliative efforts to alleviate suffering and improve quality of life, has limits; and even that our most genuine personal presence in warm-hearted consolation, can only reduce the burden so far. We must let go. (249) If we can manage to not let the fear of death hinder our recognition of the patient as dying, this in turn could promote the palliative adaptation of drug therapy, and other aspects of care depending on this recognition. In support of this last point, self-reports from hospital doctors confirm that awareness of impending death is correlated with more communication with patients and family. (250) Doctors must embrace uncertainty to cope with it. (251, 252)

The highly-selected group of people working in EOL care may, with the right coping skills and self-care strategies, also experience rewards of facing existential challenges. (126) Simply relying on disengagement and professional distance for self-care may impair communication and make patient encounters less rewarding. (244) Nursing home doctors interviewed in Paper III described how, through compassionate engagement and revealing a shared human vulnerability, they experience facilitated communication and coping better in their jobs. Daring to be vulnerable with the patients thereby facilitated EOL care, and allowed for shared meaningful experiences. Doctors also described positive experiences of gratitude, peace, awe, and reverence by the deathbed. Potential benefits of working with the dying have also been described elsewhere. (126, 253) When viewed as an opportunity for reflection on one's own life experiences and mortality, or to find meaning and perspective, EOL care work can reward personal growth, a sense of personal accomplishment and fulfillment, greater meaning in life, an increased capacity to live in the present, appreciation for life, reduced fear of death, increased compassion, and improved quality of life. (126) Perhaps due to these potential benefits, doctors working in palliative care have low burnout levels compared to other specialties. (254)

Key to helping ourselves as health care professionals endure the existential distress, uncertainties and difficulties that we face in EOL care, is improving self-awareness of how we are affected by death and dying. (126, 166, 255, 256) But what does self-care and self-awareness involve? Studies of nurses have emphasized seeking colleague support, taking time off from work, and formal supervision. (126) According to Kearney, self-awareness involves both self-knowledge, and a "dual awareness" of simultaneous attention to the needs of the patient, the work environment, and one's own subjective experience. (257) Reflection enables learning from complex situation, both after and during experience, and may be developed with practice. (258) Useful activities to enhance self-awareness include participation in educational projects, peer-support and reflection groups, engaging in mindfulness meditation and reflective writing. (257, 259, 260)

4. Adjusting interventional strategy, relational strategy and focus of self-awareness with deteriorating prognosis

In Table 4 and Figure 4, I attempt to integrate some of the findings of the studies in this thesis in a conceptual framework of a gradually deteriorating patient condition and prognosis. For each prognostic stage, I suggest a strategical perspective for intervention / drug prescription, for relation to patient and family, and focus for the reflective practice of the doctor's self-awareness. The choice of strategy is at each stage individually adjusted by the patient's goals of care.

A phased transition of palliative care with curative treatment is commonly adopted, and probably the most appropriate model for EOL care. (261) Therefore, although I present these as discrete steps in order to accommodate findings, the conceptual and idealized steps in Figure 4 and Table 4 clearly overlap. They are not a comprehensive instruction for prescription, communication and decision-making, nor for self-reflection in EOL care. Table 4 presents a selection of concepts that I can relate to the findings of this thesis, particularly to paper III. I focus on interventional strategies on drug therapy, as non-pharmacological interventions have not been studied this thesis. The figures do not incorporate the phase of bereavement care that mainly comes after death, for reasons of simplicity, and as this phase has not been the focus of this thesis.

On admission to LTC in the nursing home, the patient has an average prognosis of months to years. Both curative and preventive treatments may generally be appropriate, but the nursing home doctor needs to reconsider preventive drug treatment in the light of limited prognosis and the patient's wishes. Early ACP conversations involve getting to know the patient and family, and where they stand with respect to accepting their condition and outlook on life, and what issues are important to them at this point. Based on the latter, the ward strives to provide a meaningful environment, activities and level of stimuli. I propose that a relevant focus for self-reflective practice is the stigma of death elicited by raising the issue of dying with patient and family, and the meaning of dignity for patient, family, and doctor/staff.

As the illness trajectory moves on, for example by worsening of pulmonary, cognitive or cardiac function that may be either gradual or fluctuating, there is a supportive aim in treatment. The patient's goals of care are translated by the doctor into concrete medical options, considerately informing and negotiating with patient/family. Most preventive medicines should be discontinued by now, and efforts are made to reduce medication and intervention load. Infections are treated by antibiotics, but perhaps not intravenously, and hospitalizations are generally avoided. Treatment negotiations may be difficult. I suggest as a focus for self-reflection the impact of difficult treatment compromises made with family, on the doctor's idea of a professional conduct.

When either the patient is recognized as in the final days of life, or has severe and specific need for symptom control, doctor and staff do not give up on the patient but to the contrary heighten their engagement, concentrating their attention on close symptom monitoring, providing patient/family with information and support, striving for care goal implementation and adherence. Palliative attempts may fail, and the patient will sooner or later deteriorate further. Promises may have been made to family that cannot be kept. I suggest that a useful focus for self-reflection at this stage is the personal impact of failed palliative attempts and promises, ensuing feelings of powerlessness, the need for control, and how the doctor should and should not take responsibility for the course of illness.

Table 4. Interventional strategy, relational strategy and focus of self-awareness with deteriorating prognosis.

Prognosis	Years - months	Months - weeks	Days	Hours - minutes
Treatment aim	Curative / preventive	Curative / supportive	Specific palliative	Unmedicalized palliative
Interventional / prescription strategy	Reconsider preventive therapies (e.g. statins, anti-hypertensives, antidiabetics)	Support / normalize physiological function (e.g. diuretics, antibiotics)	Symptomatic alleviation and comfort (e.g. opioid for pain and breathlessness)	Non-intervention. Sedation for refractory symptoms
Relational strategy with patient/family	ACP / patient and family preparation	Considerate treatment negotiation	Engagement. Information and support, care goal adherence	Peaceful presence
Focus of self-awareness for the doctor	The stigma of death. Dignity of patient, family, self.	The balance of treatment compromises with professional conduct	Powerlessness and the need for control Responsibility for the course of illness	Vulnerability to death The balance of personal commitment and protective disengagement

The final moments of life are powerful and evocative. The patient's condition is clearly poor and death is likely imminent within hours. A non-intervention strategy may be applied to treatment, relationship with patient and family, and as a focus for

self-awareness. A strategy of non-intervention does not mean abandoning symptom control, or disengagement from the patient and family. Care at this stage is, more than ever, receptive to the needs of the patient and family. However, there may be a shared acceptance between family and staff to let "nature take its course", respecting the dying phase as a natural and unmedicalized part of life. Pharmacological interventions should be stable, new interventions preferably avoided, and the doctor's efforts concentrated upon availability to family and staff for information and assessment, and securing appropriate anticipatory prescribing. In the case of refractory symptoms, sedation may be an option. Palliative sedation, by dulling all experience regardless of nature, runs the risk of representing over-treatment. However, to the extent that the patient already has reduced consciousness, sedation seems a little invasive intervention. I suggest that the ideal relational strategy with patient and family in such a situation, where neither words nor medical interventions suffice or even are required, is that of peaceful presence. Such presence embodies a doctor who has reflected on his or her personal vulnerability to death, and how personal commitment to and protective disengagement from patient and family may be balanced.

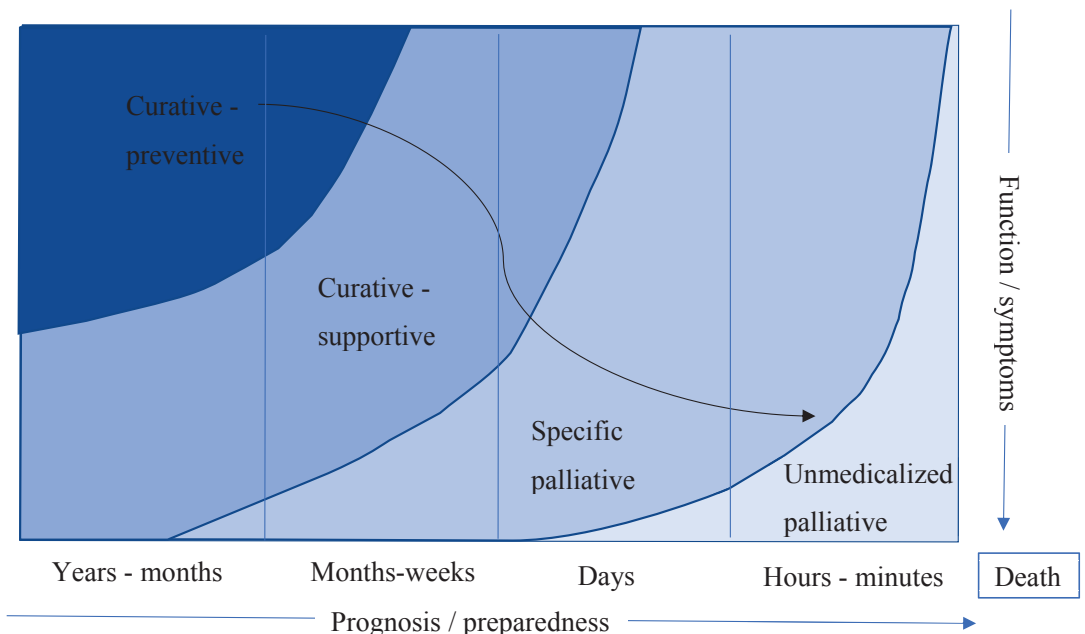Figure 4. Preparing for death – a continuum of care

Figure 4 illustrates how a patient illness trajectory (wavy arrow) moves through changes in the EOL care treatment aim, from a curative/preventive, to a curative/supportive, to a specific palliative, to an unmedicalized palliative care one. On the y-axis is objectively worsening patient condition as measured by function and symptoms toward death.

On the x-axis are two subjective measures related to the perception of distance to death: deteriorating prognosis, as subjectively assessed by the doctor; and the degree of preparedness for death of patient, family, or the doctor/staff/carer. The figure implies that both the prognosis but also the degree of preparedness of patient, family, and doctor has implications for the treatment aim. The less prepared for death either the patient, family, or doctor is, the more difficult it will be to move the care goal in a palliative direction.

Preparedness has been studied with respect to informal caregivers such as family, (242) and somewhat less with respect to health care providers. (262-264) I propose that preparedness for death is a suitable guiding concept as the aim for all three mentioned lines of care strategy: interventional strategy, relational strategy with patient and family, and focus of self-awareness. Preparedness at the level of medical intervention implies making timely adjustments to medications, aided by prognostic tools, discontinuing irrelevant treatment, and providing anticipatory symptom control therapy as-needed, ideally avoiding last-minute changes to treatment. Preparedness at the level of patient and family communication implies achieving agreement between patient, family and staff regarding the goals of care, through an integrated process of considerate treatment negotiations, and helping patient and family in their readiness for death. And when nothing else can be done or said, acknowledge this in peaceful presence. Preparedness at a personal level means self-awareness, practicing toward an "open awareness" and "courageous acceptance of death", such as what Kissane suggests as an adaptive response to the existential anxiety of death. (131)

6. Conclusions

Paper I adds to knowledge on EOL prescribing practices in nursing homes:

- Palliative EOL drugs were commonly prescribed for nursing home patients during the last days of life.

- Drug therapy changes were particularly common on the day of death.

- A diagnosis of cancer and length of stay were associated with palliative EOL drug therapy on the day of death.

Paper II adds to knowledge concerning the effectiveness and safety of drug therapy for symptomatic relief in the dying:

- Evidence still does not support the standard use of anticholinergic drugs in the treatment of death rattle.
- Some evidence supports the use of morphine and midazolam for dyspnea, anxiety, or terminal restlessness.
- Limited evidence guides the choice of opioids for pain.

Paper III adds to the understanding of nursing home doctors' experiences in EOL care and how existential vulnerability impacts their work in EOL care. Feeling at times powerless before the palliative and communicative challenges surrounding death, doctors balance both personal commitment with protective distance, as well as treatment compromises with their sense of professional conduct, in an arduous, integrated process of decision-making and grief work.

7. Implications for practice and research

Abundant drug therapy changes on the day of death point to a potential for better preparations for death in the nursing home. Characteristics of the nursing home setting and of the patient group challenge prognostication of dying. The doctor has a responsibility to promote preparedness for death both in patient, family and in himself/herself. Care may improve when there is time to get to know the patient and family.

The lack of evidence of palliative drug treatment in the dying questions doctors' ability to effectively and safely alleviate symptoms in a population that may respond differently to all drug treatments, and yet where patients and family are often reassured with the argument that this can be done. Left with few evidence based options of intervention in the last days and hours of life, efforts to communicate with and prepare patient and family for the likely symptoms of the dying phase become increasingly important. Researchers are particularly urged to include patients with non-malignant disease in clinical trials, and to conduct further high quality clinical trials on pain treatment in the dying.

Existential vulnerability plays an important role in understanding EOL care communication and in furthering professional self-care and reflection. Professional conduct in EOL care needs to take into consideration both the doctor's vulnerability as well as that of the patient and next-of-kin. EOL care training for nursing home doctors may benefit from including systematic self-reflective practice, in particular addressing treatment compromises and professional conduct in the EOL dialogue with patient and next-of-kin.

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Papers

ORIGINAL ARTICLE

Drug treatment at the end of life: An epidemiologic study in nursing homes

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Abstract

Objective. To examine drug treatment in nursing home patients at the end of life, and identify predictors of palliative drug therapy. *Design.* A historical cohort study. *Setting.* Three urban nursing homes in Norway. *Subjects.* All patients admitted from January 2008 and deceased before February 2013. *Main outcome measures.* Drug prescriptions, diagnoses, and demographic data were collected from electronic patient records. Palliative end-of-life drug treatment was defined on the basis of indication, drug, and formulation. *Results.* 524 patients were included, median (range) age at death 86 (19–104) years, 59% women. On the day of death, 99.4% of the study population had active prescriptions; 74.2% had palliative drugs either alone (26.9%) or concomitantly with curative/preventive drugs (47.3%). Palliative drugs were associated with nursing home, length of stay > 16 months (AOR 2.10, 95% CI 1.12–3.94), age (1.03, 1.005–1.05), and a diagnosis of cancer (2.12, 1.19–3.76). Most initiations of palliative drugs and withdrawals of curative/preventive drugs took place on the day of death. *Conclusion.* Palliative drug therapy and drug therapy changes are common for nursing home patients on the last day of life. Improvements in end-of-life care in nursing homes imply addressing prognostication and earlier response to palliative needs.

Key Words: *Drug therapy, end of life care, general practice, Norway, nursing homes, palliation*

Introduction

In Norway, 47.5% of deaths occur in nursing homes (NHs), 32.5% in hospitals, and 14.5% at home [1]. About 95% of patients in long-term care will die in the institution [2]. NH patients are prescribed a wider range of medications than any other subpopulation [3,4]. For the dying patient, standing drug treatments must be reconsidered and often discontinued. The last days of life are often characterized by symptoms such as pain, respiratory distress, and anxiety, as well as inability to take oral medications [5]. These symptoms may be palliated by parenterally administered drugs [6].

Whereas palliative literature has a main focus on specialized care for patients with cancer in hospice and hospital, including a range of drug therapy options for the dying [6–8], international consensus on palliative end-of-life (EOL) drug treatment for more heterogeneous NH populations is lacking. Derived from international and Norwegian guidelines [6–8], a shorter drug list has been recommended for use in NHs in Norway, comprising parenteral morphine, benzodiazepines, anticholinergics, and antipsychotics [2,5]. Previous studies on EOL care in NHs have reported on treatment with selected drug groups such as opioids and pulmonary agents [9], and pain relief [4] without a clearly defined palliative drug treatment.

Pharmacological treatment for dying patients is thus an important aspect of EOL care in NHs, of which we have little knowledge. Insight into initiation and discontinuation of drug therapy in this phase may shed light on the quality of EOL care and point to vulnerable patient groups. Our study aimed to examine drug treatment in NH patients at the EOL, and to identify predictors of a clearly defined palliative drug therapy.

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End-of-life care guidelines are centred on cancer patients, while nursing home patients die from various illnesses.

- This study shows that palliative drugs were commonly prescribed for nursing home patients during the last days of life.
- A diagnosis of cancer and length of stay were associated with palliative drug therapy.
- Most initiations of palliative drugs, and most withdrawals of curative/preventive drug therapy, occurred on the day of death.

Material and methods

Study population

NHs in Norway accommodate around 41 000 beds, corresponding to 18% of the general population 80 years and older. All NHs provide EOL care, but only 42 institutions have specialized palliative care units. Most NH physicians in Norway are part-time engaged general practitioners [1]. The study population comprised all patients in three urban NHs in Norway admitted from January 2008 and deceased before February 2013. The institutions were selected on the basis of using an electronic patient record system optimized for data extraction [10].

Data collection

We collected routinely registered data from the patients' final NH stay: demographic data (age, gender, date of NH admission and death, long- or short-term stay); diagnoses (ICD-10) [11]; medications (generic name, Anatomical Therapeutic Chemical (ATC) code [12], drug formulation, regular or as-needed schedule, indication, dates of initiation, alteration, or discontinuation). An external IT consultant extracted the data, and replaced ID-numbers with a running number, the key to which remained undisclosed to the research group.

Drug therapy

We defined palliative EOL drug therapy in NHs on the basis of indication, drug, and formulation; (1) any drug prescription with an explicit EOL care indication key word was included: palliative, terminal, death, death rattle, Liverpool Care Pathway, or EOL; (2) we also included prescriptions of specifically recommended *injectable* palliative EOL drugs for use in NHs [2,5], regardless of missing EOL key words in the indication text (Table I). "Curative/ preventive drug therapy", in contrast, was defined as medication for regular use without an explicit EOL care indication.

Statistical analysis

User rates were established for drugs according to the above categories. We explored predictors of palliative EOL drug therapy by a chi-squared test, and subsequently by binary logistic regression analysis; dependent variable: palliative EOL drug therapy; independent variables: age, gender, length of stay, nursing home, diagnosis of cancer. All variables but age were analysed as categorical. Significance was determined at a level of 5%. IBM SPSS Statistics 20 (SPSS Inc., Chicago, Ill., USA) was used for statistical analyses.

Results

Patient characteristics

The study population comprised 524 deceased patients. Median (range) age at death was 86 (19–104) years, 59.4% were women, 68.1% in long-term care. The most common registered diagnoses were dementia (36.8% of the patients), congestive heart failure (29.6%), and cancer (23.7%) (Table II).

The three NH populations did not differ with regard to gender or number of diagnoses. Compared with the other NHs, more patients at NH C were 86 years and older, or had a diagnosis of infection or cancer, $p < 0.01$. Patients at NH A had longer stays

Table I. Injectable drugs recommended for palliative treatment for the dying in NHs in Norway [2,5], by proportion (%) of users on the day of death.

Drug name	ATC code	Common EOL use	Proportion (%) of patients
Morphine	N02AA01	Pain or dyspnoea	71.4
Glycopyrronium	A03AB02	Death rattle	46.9
Scopolamine	N05CM05	Death rattle	25.8
Morphine-scopolamine	N02AG01	Pain or dyspnoea and death rattle	12.2
Midazolam	N05CD08	Anxiety, agitation	55.0
Diazepam	N05BA01	Anxiety, agitation	1.0
Haloperidol	N05AD01	Nausea and terminal delirium	46.9

Table II. Patient characteristics (n = 524).

Median (range) age at death, years	86 (19–104)
Women, %	59.4
Median (range) length of stay, days	103 (0–1765)
Long-term care, %	68.1
Diagnoses:	
Dementia, %	36.8
Congestive heart failure, %	29.6
Cancer, %	23.7
Chronic pulmonary disease, %	18.5
Infections, %	20.0
Hip fracture, %	9.7

($p < 0.01$), as the EPR data were collected from was used only in the long-term ward.

Patients with cancer more frequently died within two weeks of admission than patients without cancer (41.1% vs. 20.5%, $p < 0.01$). Patients with dementia more frequently died after stays of longer than 16 months compared with patients without this diagnosis (40.4% vs. 16.0%, $p < 0.01$).

Drug use on the day of death

On the day of death, 99.4% of the study population were on drug therapy. The most common regular and as-needed drugs are shown in Table III.

Of the 4736 standing prescriptions (regular and as-needed drugs) on the day of death, palliative EOL drugs comprised 1306 (27.6%) and curative/preventive drugs 2419 (51.1%), while 1011 (21.3%)

prescriptions were not classified in either category. Indication was documented for 99.6% of all drugs on the day of death.

Altogether 50.2% of patients were prescribed any drug with a specified EOL care indication. The most common palliative EOL drugs were morphine (71.4% of patients), midazolam (55.0%), glycopyrronium (46.9%), and haloperidol (46.9%) (see Table I). Palliative EOL drugs were prescribed to 74.2% of the study population, either alone (26.9%) or concomitantly with curative/preventive drugs (47.3%). Curative/preventive drugs were prescribed to 72.5% of patients (alone 25.2%). Some 95.7% of palliative EOL drugs were prescribed as needed. Patients had standing prescriptions of median (25th–75th percentile) three (zero–eight) palliative EOL drugs and three (zero–four) curative/preventive drugs on the date of death. There was a median period of two (zero–seven) days from prescription to death for palliative EOL drugs.

Having prescriptions of palliative EOL drugs at death was associated with length of stay > 16 months (AOR 2.10, 95% CI 1.13–3.95), cancer (2.12, 1.19–3.76), age (1.03, 1.005–1.05), and being at NH B (3.53, 1.99–6.25) or NH C (4.20, 2.36–7.48) (Table IV).

Figure 1 shows that the proportion of patients for whom at least one palliative EOL drug was initiated, or at least one curative/preventive drug was discontinued, increased in the last week before death and peaked on the day of death.

Table III. Most common drugs on the date of death (% of patients).

ATC-code	Regular drugs Drug subgroup	Proportion (%) of patients	ATC-code	As-needed drugs Drug subgroup	Proportion (%) of patients
A06A	Laxatives	32.6	N02A	Opioid analgesics	82.6
N02A	Opioid analgesics	32.4	N05C	Hypnotics	70.4
N02B	Non-opioid analgesics and antipyretics	28.2	N05A	Antipsychotics	51.1
C03C	High-ceiling diuretics	26.7	N05B	Anxiolytics	30.9
B01A	Antithrombotic agents	24.0	N02B	Non-opioid analgesics and antipyretics	26.0
N06A	Antidepressants	19.1	A03A	Drugs for functional gastrointestinal disorders[1]	24.6
C07A	Beta-blocking agents	17.6	C03C	High-ceiling diuretics	16.8
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease	15.1	A03F	Metoclopramide	13.4
B03B	Vitamin B12 and folic acid	14.3	A06A	Laxatives	13.0
N05C	Hypnotics	13.5	C01D	Vasodilators used in cardiac diseases	11.1
N05A	Antipsychotics	11.5	R03A	Adrenergic inhalants	6.3
N05B	Anxiolytics	11.1	A10A	Insulins and analogues	5.2
C09A	ACE inhibitors, plain	8.6	B05B	i.v. solutions	4.8
H02A	Corticosteroids for systemic use, plain	8.4	R05C	Expectorants, excl. combinations with cough suppressants	4.6
R03A	Adrenergic inhalants	8.4	R03B	Other drugs for obstructive airways disease, inhalants	4.4

Note: [1]Glycopyrronium represented 84.8% of prescriptions in this category.

Table IV. Associations between palliative EOL drug therapy and patient characteristics.

	Proportion of patients (%) prescribed palliative drugs	Chi-square, p	AOR	95% CI
Nursing home:				
A	52.7	<0.01	1	Ref
B	78.7		3.53	1.91–6.00
C	80.4		4.20	2.26–7.08
Length of stay (quartiles):				
<2 weeks	81.2	0.01	1.86	0.97–3.25
2 weeks–3 months	65.1		1	Ref
3–16 months	71.8		1.70	0.97–3.17
>16 months	78.6		2.10	1.13–3.95
Gender:				
Women	75.8	0.31	1	Ref
Men	71.8		0.98	0.60–1.44
Age:				
86+	77.4	0.06	1.03	1.005–1.05
<86	70.0			
No. of diagnoses:				
> 6	76.6	0.21	Variable not included	
<6	71.7			
Cancer:				
No	71.5	0.01	1	Ref
Yes	83.1		2.12	1.30–4.13
Dementia:				
No	72.2	0.16	1	Ref
Yes	77.7		1.43	0.88–2.25
Infections:				
No	75.4	0.22	Variable not included	
Yes	69.5			
Chronic pulmonary disease:				
No	75.2	0.30	Variable not included	
Yes	70.1			
Heart failure:				
No	73.4	0.52	Variable not included	
Yes	76.1			
Hip fracture:				
No	74.6	0.53	Variable not included	
Yes	70.6			

Notes: Logistic regression model: chi-squared $(8, 524) = 58.41$, $p < 0.001$, Cox & Snell $R2 = 0.11$, 74.4% correctly classified. The logistic regression was performed as a block analysis, each variable being adjusted by the effects of the others. Association strength is given as adjusted odds ratios (AORs), with 95% confidence intervals (CI). Only variables with a $p < 0.20$ in the chi-squared test were included in the regression analysis, with the exception of gender which was included on the basis of being a common confounder. In the regression model, age was analysed as a continuous variable, all other included variables as categorical. Ref = reference value.

Discussion

Our study shows that palliative EOL drugs were commonly prescribed for NH patients during the last days of life. NH, a diagnosis of cancer, and long stay were associated with palliative EOL drug therapy. Most initiations of palliative EOL drugs, and most withdrawals of curative/preventive drug therapy, occurred on the day of death.

Strengths and weaknesses

The study population comprised patients from all types of wards, and although the diagnostic data are

not validated this broad diversity is expected to reflect NH populations in general.

With the exception of short-term care patients from NH A, all patients admitted and deceased in three NHs during the five-year study period were included, limiting selection bias. Only three institutions participated in the study, limiting statistical power and to some extent generalizability.

A complete set of medication data for all patients was collected. The electronic patient record did not include information on whether prescribed medication was actually taken, leading to possible overestimation of drug use. Prescribed medication, on the
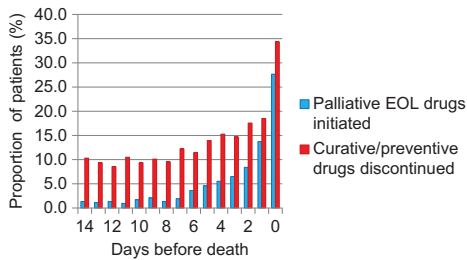
Figure 1. Proportion of patients (%) for whom at least one palliative EOL drug was initiated, or at least one curative/preventive drug was discontinued during the last 14 days of life.

other hand, may reflect the doctor's treatment decisions more appropriately than given medication. This point is particularly important for palliative drugs, which comprised almost exclusively as-needed drug prescriptions.

Use of indication text secured a comprehensive definition of palliative EOL drugs, while inclusion of specifically recommended palliative EOL drugs ensured that these prescriptions were not missed regardless of missing EOL key words in the indication text. Restricting the latter to injectables, we excluded prescriptions less specific to the dying patient, such as opioid tablets, oral suspensions, and patches. Injectable antipsychotics and benzodiazepines may on occasion be used to treat neuropsychiatric symptoms in dementia. A median of two days from prescription to death makes it less likely, though, that these prescriptions were issued for their non-palliative indications. Although anticholinergics have other indications, in injectable form, glycopyrronium and scopolamine are seldom used for non-palliative purposes in NHs.

Comparison with other studies

There are few other studies reporting on drug therapy at the EOL in the general NH population, and with considerably smaller sample sizes. Decreased overall treatment intensity has been found in patients perceived as dying, across NH, hospital, and general practice settings in the Netherlands [13]. Patients with dementia dying in American NHs were prescribed unchanged total numbers of drugs, palliative medications replacing other medications [9].

Our study adds to previous knowledge showing that NH patients with the longest duration of stay, or a diagnosis of cancer, were more likely to receive palliative EOL drugs on the day of death than those without these characteristics. More than 80% of long-term care patients have dementia [14], interfering

with the communication of suffering, analgesia, and EOL care [15–17]. Accurate survival prediction for patients with advanced dementia is difficult, and may hinder palliative care [18]. Longer NH stays may nevertheless allow time for advance care planning and staff familiarity with the patient, thus facilitating palliation, and perhaps explaining the association found with the longest stays. Patients with cancer often have expected deaths with a typically rapid functional decline, and are at the centre of palliative guidelines [7,19]. Palliative drug therapy for this group was therefore expected. A diagnosis of dementia, heart failure, chronic pulmonary disease, infection, or hip fracture was not associated with initiation of palliative drugs. This may indicate death coming unexpectedly. For respiratory distress in chronic pulmonary disease there may also be a reservation among physicians to prescribe morphine and benzodiazepines, as they inhibit respiration.

An evidence base for EOL care in non-malignant conditions, which are prevalent in the general NH population, is scarce [20]. We found a high treatment rate with palliative drugs (73.9% overall, 71.9% for morphine), in line with 77% of NH patients with advanced dementia in the Netherlands receiving opioids. Despite extensive prescribing, the Dutch study found that symptoms of pain, shortness of breath, and agitation were prevalent, suggesting that a prescribed drug is no guarantee of satisfactory symptom control [21]. For this, factors such as close symptom assessment as well as appropriate drug dosage and administration are required.

Palliative drug therapy increased and curative/preventive drug treatment decreased in the last week of life, most changes taking place on the day of death. A recent study in long-term care facilities in Canada found that care only changed substantially to palliative in nature during the last hours or days of life, calling for earlier awareness of impending death [22]. Initiation of palliative drugs is not to be expected for all dying patients, nor does it depend only on staff competence. Less palliative drug therapy could also come from less need for it, by having a shorter terminal phase, or less burdensome symptoms. Little is known about the identification and duration of the dying phase in NH patients and for how many it lasts long enough to allow for pharmacological response. Distinct death trajectories have been described for patients with different diseases [23], and timing of palliative care for patients with non-malignant diagnoses has been shown to be particularly challenging [24]. Yet, relatively accurate prediction of survival for these patients in NHs has been shown to be feasible, though only in the last seven days of life [25].

NH A had a lower proportion of patients prescribed palliative medications at death. Differences

in prescribing culture between doctors may be one explanation. For the present study we did not collect this variable.

Meaning of the study

Palliative drug prescriptions and drug therapy changes are common for NH patients on the last day of life. Extensive curative/preventive drug therapy and comprehensive changes in drug treatment on the day of death may both point to the known prognostication difficulties in the multimorbidity characterizing NH populations. Improvements of EOL care in NHs must address prognostication and an early response to palliative needs.

Acknowledgements

Ethical approval

The Regional Committee for Medical and Health Research Ethics (2012/1748), and Norwegian Social Science Data Services (12/30691) approved the study.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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II

Safety and effectiveness of palliative drug treatment in the last days of life - a systematic literature review

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Figures: 1
References: 68
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ABSTRACT

Context. Dying patients commonly experience potentially distressing symptoms. Palliative care guidelines recommend opioids, anticholinergics, antipsychotics and benzodiazepines for symptom relief.

Objectives. To systematically review the effectiveness and safety of palliative drug treatment in the last days of life of adult patients, focusing on the management of pain, dyspnea, anxiety, restlessness, and death rattle.

Methods. A systematic search of the literature published before December 2016 in PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, ClinicalTrials.gov, and SveMed+. Studies on safety or effectiveness of drug therapy in dying adults with at least one outcome on symptom control, adverse effects, or survival were included. Data for included studies were extracted. Study quality was assessed using the Effective Public Health Practice Quality assessment tool for quantitative studies.

Results. Of 5940 unique titles identified, 12 studies met the inclusion criteria. Five studies assessed anticholinergics for death rattle, providing no evidence that scopolamine hydrobromide and atropine were superior to placebo. Five studies examined drugs for dyspnea, anxiety, or terminal restlessness, providing some evidence supporting the use of morphine and midazolam. Two studies examined opioids for pain, providing some support for morphine, diamorphine and fentanyl. Eight studies included safety outcomes, revealing no important differences in adverse effects between the interventions, and no evidence for midazolam shortening survival.

Conclusion. There is a lack of evidence concerning the effectiveness and safety of palliative drug treatment in dying patients, and the reviewed evidence provides limited guidance for clinicians to assist in a distinct and significant phase of life.

Running Title: Drug safety and effectiveness in the dying

INTRODUCTION

Dying patients, in the last hours and days of life, commonly experience pain, dyspnea (breathlessness), anxiety, restlessness, and death rattle (noisy respiratory secretions in the dying). (1-3) Patients at this stage are often referred to as "actively dying", with a clinical presentation of waning physiologic functions converging across diagnoses. (4) Drug therapy, such as opioids for pain and dyspnea, anticholinergics for death rattle, antipsychotics for agitated delirium, and benzodiazepines for anxiety, is recommended in palliative care guidelines internationally. (5-13)

The dying patient is affected by a state of physiological multi-organ failure, which in a number of ways may impact the effectiveness and adverse effects of drug therapy. (14) Patients may additionally be unable to self-report symptoms or participate in treatment decisions due to reduced consciousness, and proxy assessments based on observations of physical and behavioral factors may diverge from patient experience. (15) Lastly, palliative drug therapy for dying patients should neither prolong suffering nor shorten life. (16)

The effectiveness and safety of drug therapy used for palliation in the dying patient have been most extensively studied in patients with terminal cancer. Extrapolation of data from populations with cancer to other populations has a number of issues. Most patients die from conditions other than cancer. (17) The illness trajectory may be more unpredictable in non-malignant conditions, (18) with unique patterns of distress (19) affecting prognostication (20) and treatment. (21) Adding complexity to this, the choice to use palliative drug therapy is not only a purely medical decision, but typically subject to shared decision-making (22) under the influence of interpersonal, psychological, organizational and cultural factors. For example, initiation of drug treatment at the end of life is affected by negotiations with the patient's family, and the physician's own existential encounter with death. (23) Dialogue between doctor, staff, patient and family in order to adjust aims of treatment and care and to support shared decision-making is known as Advance Care Planning (ACP), (24, 25) a process which may or may not result in written directives specifically instructing treatment, often referred to as "advance directives", (26) "living wills" or "physician/medical treatment orders". (27)

The 2015 NICE guidelines on Care of dying adults in the last days of life (5) reviewed comparative studies on symptomatic drug treatment in the last 14 days of life. The NICE guidelines report one study on drug treatment of pain, three studies on breathlessness, three studies on nausea, and eight studies on respiratory tract secretions. However, for the treatment of other common symptoms in dying persons, such as anxiety, delirium or agitation no

evidence is provided in the NICE guidelines or in two earlier Cochrane reviews on a broader palliative care population. (28, 29)

This study aims to systematically review the effectiveness and safety of palliative drug treatment in the last days of life of adult patients, focusing on the management of pain, dyspnea, anxiety, restlessness, nausea and death rattle.

METHODS

This study was registered in the PROSPERO International prospective register of systematic reviews (CRD42016029236) and conducted in accordance with the PRISMA guidelines (see Appendix 1 for the PRISMA checklist).

Search strategy

We conducted a systematic search in PubMed/MEDLINE, Embase, CINAHL, PsycINFO, Cochrane, ClinicalTrials.gov, and SveMed+. The search strategy (see Appendix 2 for the Search strategy) was adapted from a strategy presented in the 2015 NICE Guidelines Care of the dying adult (A.2.1 Recognising dying). (5) In addition, we hand-searched the reference lists of all included articles and relevant literature reviews.

Inclusion/exclusion criteria

Studies were included in the review if they used an experimental or quasi-experimental design (clinical trial, cohort, or case-control) to examine the effectiveness or safety of palliative drug therapy in adults (≥18 years) in their last two weeks of life or clinically considered dying. All settings, countries and diagnoses were included. Any comparison groups, or the lack of, were accepted. Qualitative studies, case reports, cross-sectional studies, opinion pieces and conference abstracts were excluded. We did not restrict our search by publication date, as we anticipated few high-quality studies. Studies were restricted to English, Spanish, German, French, Norwegian, Swedish, Danish, and Dutch languages, for the authors to be able to assess them. Studies that did not focus on the specified primary or secondary outcomes of interest listed below were excluded.

Outcomes of interest

- Primary outcomes: symptom or symptom control measures regarding pain, dyspnea, anxiety, restlessness, and death rattle; number or degree of adverse effects; and mortality or survival.
- Secondary outcomes: level of consciousness, functional level, quality of life, and quality of care.

Study selection and data extraction

After removal of all duplicates, studies were evaluated in a stepwise procedure for inclusion in the review (Figure 1). All titles identified in the search were screened for eligibility. For those titles considered potentially eligible, the abstracts were screened independently by two authors (KJ and LP), using the inclusion criteria specified above. The full text of all articles meeting these criteria was assessed independently by pairs of authors (KJ and DFH, KJ and LP, or KJ and SR). For the 12 articles meeting the inclusion criteria, data extraction was performed using the McMaster Critical Review Form for quantitative studies. (30) Additional information on health care setting, time before death studied, diagnostic category, drug category, and drug administration route was also extracted. To test the study selection and data extraction processes, a pilot assessment and data extraction were made by all authors on five studies. Discrepancies were resolved via discussion between author pairs until agreement, or referred to at least one other review author for consensus.

Quality assessment

The quality of the 12 studies included in the review was assessed using the Effective Public Health Practice (EPHPP) Quality assessment tool for quantitative studies. (31) This tool was chosen for its applicability across a wide range of quantitative study designs. Studies were rated weak, moderate or strong on the following six components: selection bias, study design, confounders, blinding, data collection, and withdrawal. The quality ratings across the six domains were aggregated to give a global rating for each study as follows: weak (two or more component weak ratings), moderate (one weak rating), or strong (no weak ratings). Quality assessments were scored independently by three authors (KJ, DFH, and SR), and discrepancies discussed until consensus was reached. Bias was further discussed at an outcome level where considered relevant.

RESULTS

Final search date was the 21st of December 2016. Our search identified 5923 records. After removal of 1720 duplicates, we screened 4203 unique titles, and 819 potentially relevant abstracts, yielding 70 records that met the inclusion criteria. Following full-text assessment of these, 9 articles were included for data extraction. Hand searching the reference lists of the included studies as well as those of 18 systematic reviews and five review articles identified

in the initial search, we identified three additional studies, (32-34) for a total of 12 studies (Figure 1). Heterogeneity of studies did not allow for meta-analysis.

Study characteristics

The 12 studies included for data extraction were published between 1977 and 2016 (Table 1). Eight studies were performed in Europe, (32-39) two in North America, (40, 41) one in Asia (42) and one in South America. (43) Seven studies were randomized controlled trials (RCTs), (32-36, 40, 43) four were prospective cohort studies (37, 38, 41, 42) and one a retrospective cohort study. (39) Eight studies were set in palliative care units or hospices; (34-41) with one of these also including home care patients. (41) The remaining four studies were set at non-specialist palliative care hospital wards. (32, 33, 42, 43) All studies were either exclusively or predominantly conducted in patients with a main diagnosis of cancer. The time before death studied was, in all studies except one where it was not reported, (40) either expressed in terms of time from study entry to death, or as a life expectancy estimate (Table 1).

The studies included a range of different palliative drug treatments. Five studies investigated anticholinergics, (32, 35-37, 40) five studies opioids, (33, 34, 39, 42, 43) three studies benzodiazepines, (33, 38, 43) and one study investigated an antipsychotic; (41) seven of the studies evaluated more than one drug. (33-37, 39, 43) Five studies looked at death rattle, (32, 35-37, 40) five studies at dyspnea, (33, 38, 41-43) and two studies looked at pain. (34, 39) Three of the studies on dyspnea also investigated restlessness, (41) delirium (38) or anxiety. (43) Overall, seven included studies reported on adverse effects, (33-36, 40, 42, 43) and three studies reported comparatively on survival. (33, 36, 38) Data on all primary outcomes (symptom control, adverse effects, and survival) were identified. The only secondary outcome discussed in the included studies was level of consciousness. No data on impact of palliative drug therapy on functional level, quality of life or quality of care were identified.

Quality assessment

The EPHPP global rating scores for the quality of the included articles are presented in Table 2. Two articles were rated as "strong", seven articles were rated "moderate", and three articles were rated "weak". The most common weak component ratings were for confounders, (33, 39, 41, 42) data collection, (39, 41, 43) blinding, (36, 38, 42) and withdrawal. (34, 35, 42)

Death rattle

Study characteristics. Five studies examined the effectiveness of anticholinergics for death rattle (Table 3). The drugs studied were scopolamine butylbromide, scopolamine hydrobromide, glycopyrronium hydrobromide, and atropine. Four studies were RCTs, (32, 35, 36, 40) two of which were placebo-controlled, (32, 40) and one of which was a pilot RCT; (35) one study had a prospective cohort design. (37) Study quality was assessed as strong in two studies, (37, 40) and moderate in three. (32, 35, 36) Three studies (36, 37, 40) used a scoring scale as proposed by Back et al. (37) to assess the severity of death rattle (0, inaudible; 1, audible only very close to the patient; 2, clearly audible at the end of the bed, in a quiet room; 3, clearly audible at about 20 ft (9.5 m), in a quiet room).

Comparison with placebo. No drugs tested against placebo (scopolamine hydrobromide and atropine) were found to be superior to placebo. A placebo-controlled RCT from the USA comparing sublingual atropine to sublingual saline in 160 patients found no difference in noise score and heart rate at baseline, after 2 hours (p=0.73) and 4 hours (p=0.21). (40) A smaller placebo-controlled study from Germany compared intravenous (i.v.) or subcutaneous (s.c.) scopolamine hydrobromide to saline in 31 patients, and likewise found no significant difference in death rattle scores (p value not reported). (32)

Comparison between drugs. Three head to head studies compared the effectiveness of different anticholinergics, with conflicting evidence regarding comparative effectiveness. A small double-blinded pilot RCT from Germany (n=13) comparing the effect of i.v. scopolamine hydrobromide and glycopyrronium found significantly less death rattle with glycopyrronium. (35) No difference in restlessness and expressions of pain was found between the two groups. Neither of the two German studies were powered to show a difference between groups, and results were presented as figures, with no percentages shown. (32, 35) An RCT from Belgium (n=333) revealed that s.c. atropine, scopolamine butylbromide and scopolamine hydrobromide reduced noise score in around 40% of cases, with no significant difference between the drugs. (36) In considering this outcome, it should be noted that the study was not blinded, and there was no systematic recording of intravenous and oral fluid intake, which could have influenced the development of the death rattle. A prospective cohort study from the UK (n=170) revealed significantly more patients with reduced death rattle noise scores 30 minutes after injection of scopolamine butylbromide (p=0.002), and less need for a second injection (p=0.03) compared with glycopyrronium. (37) The dose of glycopyrronium was not quite equipotent (0.20 mg given, 0.27 mg needed) to the scopolamine butylbromide dose, possibly influencing the findings. No important differences

in adverse effects or survival were noted in the studies, although the Belgian study noted a temporarily decreased consciousness with scopolamine hydrobromide compared to atropine and scopolamine butylbromide after 12 hours (P=0.0076) but not after 24 hours.

Dyspnea

Study characteristics. Five studies investigated the effectiveness of drug therapy for dyspnea, either alone (33, 42) or in combination with anxiety, (43) agitated delirium (38) or terminal restlessness (41)Three of the studies reported also on safety outcomes (Table 2). (33, 42 , 43) Drugs studied were the opioids morphine (33, 43) and fentanyl, (42) the benzodiazepine midazolam, (33, 38, 43) and the antipsychotic chlorpromazine. (41) Two studies were RCTs, (33, 43) and three were prospective cohort studies. (38, 41, 42) Study quality was assessed as weak in two studies, (41, 42) and moderate in three. (33, 38, 43)

Morphine and midazolam for dyspnea. Some evidence was found to support the use of morphine and midazolam for dyspnea. An RCT from Argentina (n=51) compared s.c. morphine plus midazolam (MM) versus oxygen. (43) Based on a verbal rating scale, significant dyspnea improvement was found in both groups, in favor of MM at 24 hours (p=0.03). Nausea was reported for both groups. An RCT from Italy (n=101) also found more patients experiencing dyspnea relief according to a modified Borg scale in the continuous s.c. MM group compared to the morphine (p=0.03) or midazolam (p=0.0004) alone groups after 24 hours, a benefit which after 48 hours only stayed significantly different compared to midazolam alone (p=0.04). (33) Somnolence was more frequent in the morphine group. Navigante et al. attribute the somnolence to the frequent episodes of breakthrough dyspnea in this group being treated by higher doses of midazolam compared to the two other groups, in the form of frequent midazolam rescue doses. This study also had a high attrition rate due to deaths within the observation period of 48 hours (31/101). No significant difference in survival between the groups was noted.

Fentanyl for dyspnea. A small uncontrolled prospective cohort study from Singapore (n=16) found no effectiveness of i.v. fentanyl to relieve dyspnea. (42) Based on self-reported dyspnea severity after 24 hours compared with severity at infusion start, no significant difference was found between the proportion of non-responders versus responders (56.3% vs 43.8%, p=0.33). Few adverse effects were reported. Although five patients did not die within the same hospital admission, mean survival for deceased patients was 7 days. Also, 20

patients dropped out, being too ill to self-report symptoms, or dying before 24 hours, rendering this a dying population for the purposes of this study.

Anxiety

Some evidence was also found to support the use of morphine and midazolam for anxiety. The above mentioned RCT from Argentina (n=51) compared s.c. morphine plus midazolam (MM) versus oxygen for anxiety. (43) An improvement in anxiety was observed for both groups at 20 min, but after 24 hours only in the MM group (p=0.035), MM performing better than oxygen both at 20 minutes (p=0.024) and 24 hours (p=0.032).

Terminal restlessness

Two studies investigated the effectiveness of drug therapy on agitated delirium or terminal restlessness. (38, 41) A prospective cohort study from Italy supported the use of midazolam for agitated delirium. (38) Continuous i.v. midazolam given as a sedation regimen in 42 patients gave less symptoms (p=0.0001) with increasing drug doses. (38) There was no control group for the effect outcomes and we assessed the study quality as weak. Survival from admission in patients sedated with midazolam was longer compared with a control group that was not sedated (p=0.003), but details of the drug treatment and the condition of unsedated patients were not reported, and there may have been a selection bias.

An uncontrolled prospective cohort study for the effectiveness of i.v./rectal chlorpromazine sedation on dyspnea (10 patients) and restlessness (10 patients) included both palliative care inpatients and outpatients in the USA. The study did not discriminate effectiveness results with respect to the two symptoms included, but reported complete symptom relief in 18/20 patients and partial relief in 2/20 patients before death. (41) Although McIver et al. concluded that chlorpromazine is highly effective, the lack of control group opens for confounding, data collection tools lacked reliability and validity, and study size was small.

Pain

Our review includes two studies specifically investigating treatment of pain in the dying. (34, 39) Overall, there appears to be little evidence supporting drug treatment for pain in the dying. Oral morphine was superior to oral diamorphine in controlling pain in male patients in

one RCT, (34) and fentanyl patches were more effective than intravenous diamorphine in a retrospective cohort study. (39) However, the differences between groups were likely explained by confounders in both studies. In the crossover RCT on 146 patients, male patients had more pain (16.8 mm difference between group means as measured on a Visual Analogue Scale (VAS), $p<0.01$) and worse mood score (12.5 mm difference, $p<0.01$) when given diamorphine compared to when given morphine. (34) No difference was found for female patients, and results across genders were not reported. The doses of the two agents were according to the authors probably not equipotent, with 1.5 mg diamorphine hydrochloride compared to 1 mg morphine sulphate. Furthermore, there was a high attrition rate in the study with only 21% (n=146/699) of participants crossing over to receive a second agent. A retrospective cohort study comparing the effect of a fentanyl patch versus diamorphine in a syringe driver in 94 patients reported better pain control at 20 hours and 8 hours compared to the diamorphine group. In addition, the fentanyl group used fewer "as required" opioid doses on the last day of life (p=0.001). (39) Both groups had good pain control in the last 48 hours of life. Patients having fentanyl patches received approximately twice the equianalgesic dose of those receiving diamorphine and although patients were matched for age, sex, and diagnosis, fentanyl patches were considered a second-line treatment, indicating that patients treated with fentanyl patches may have had more complex pain.

DISCUSSION

This systematic review shows that despite routine use of palliative drug therapy for symptom control in dying adults, there is little evidence regarding the effectiveness and safety of the commonly used agents. Twelve studies examining the effectiveness (n=12) and safety (n=8) of palliative drug therapy across a range of symptoms were reviewed. Despite including both experimental and quasi-experimental designs the included studies were small scale and only two were considered to be of strong quality, further limiting their contribution to the evidence base of palliative drug therapy in dying adults.

Death rattle

No evidence supporting the use of anticholinergics for death rattle was found. Our review found that anticholinergics were no better than placebo for reducing death rattle. Similar findings have been previously reported in two reviews. (5, 44) Our review highlights possible safety concerns associated with the use of scopolamine hydrobromide when compared to atropine and scopolamine butylbromide, in the form of temporarily decreased consciousness.

Death rattle is a symptom with uncertain impact on the patient, not associated with respiratory distress in the patient, (45) but difficult to endure for family and staff. (46, 47). In absence of evidence and with uncertainty regarding the need for its treatment, reassuring communication with next-of-kin may be preferable. (44, 48, 49)

Dyspnea

In this review we found some evidence regarding the use of morphine and midazolam, especially in combination, for management of dyspnea in dying patients. Our results support those previously reported in the NICE review of 2015. While we found some evidence for morphine/midazolam, no evidence supporting the use of fentanyl was found. A single prospective cohort study examining the use of i.v. fentanyl was included in the review. (42) No significant response to i.v. fentanyl was reported, but the uncontrolled study design may weaken the strength of this conclusion and further studies are needed. Looking at a broader palliative care population and not just the actively dying patient, two recently updated Cochrane reviews have found no evidence supporting the use of benzodiazepines for the relief of breathlessness in people with advanced cancer and chronic obstructive pulmonary disease (COPD), (50) and only some low-quality evidence showing benefit of oral or parenteral opioids to palliate breathlessness. (51)

No major safety concerns regarding the use of morphine, midazolam or fentanyl for dyspnea in the dying were identified in this review. Adverse effects associated with the use of palliative drug therapy for dyspnea established in the broader palliative care population include drowsiness, nausea and vomiting with opioids, and somnolence with benzodiazepines. (50, 51) However, the safety of opioids for dyspnea relief is further substantiated in broader palliative care populations in a 2014 systematic review, finding no compromise of respiratory function. (52)

Anxiety

Our review identified one RCT from Argentina addressing the use of palliative drug therapy for the management of anxiety in the dying patient, finding that a combination of midazolam and morphine was more effective than the use of oxygen. (43) No studies meeting the inclusion criteria were found in the earlier NICE review, (5) nor in a Cochrane review updated in 2012 on drug therapy for anxiety in a broader palliative care population. (29)

Terminal restlessness

The present review found limited evidence supporting the use of midazolam and chlorpromazine for terminal restlessness, in two studies of palliative sedation. (38, 41) Neither study reported specifically on adverse effects, but the study by Mercadante et al. reported no reduced survival associated with the use of midazolam for palliative sedation.

A review of the evidence for treatment of delirium or agitation in the dying by NICE in 2015 (5) and a Cochrane review from 2012 (28) also found insufficient evidence to draw conclusions about the role of drug therapy in the treatment of delirium in terminally ill patients. A more recent Cochrane review from 2015 found limited evidence for the effectiveness of palliative sedation in terms of quality of life and symptom control, but did not differentiate between pharmacological agents. (53) In line with our review, the 2015 Cochrane review concluded that palliative sedation does not hasten death, a central ethical concern.

Pain

A pain-free death is a central theme for patients, family, and health-care providers when defining a "good death", (54) and pain is a common distress in the dying. (3) Our review identified only two studies addressing pain treatment in the dying. Morphine, diamorphine and fentanyl patches have been studied, but considerable confounding makes interpretation of the results problematic, limiting their contribution to the evidence-base. While palliative sedation may be indicated for refractory pain, uncontrolled pain was not an indication for sedation in the two studies included in this review, although concomitantly present in 4/42 patients in one of them. (38) Opioid studies in populations who are dying are challenging. An analgesic effect of opioids is clearly expected, making placebo controlled groups ethically unjustified. However, issues of altered absorption, metabolism and elimination of opioids in dying patients may affect treatment effectiveness and adverse effect profiles. (14, 55) Further high quality clinical trials comparing pain treatments in the dying are warranted to guide clinical practice regarding this critical issue.

Adverse effects and survival

Overall, few adverse effects were reported in the articles included in the current review, and several studies did not report on adverse effects at all. One explanation may be that the distinction of therapeutic versus adverse drug effects may be unclear in the actively dying patient. In particular, a sedative effect may be an adverse effect when an opioid is given to alleviate pain, but therapeutic when midazolam is given for restlessness or anxiety. The

relative sedative impact is also lesser if the patient's level of consciousness is already decreased. In addition, although some adverse effects have obvious objective presentations such as injection site redness, vomiting or respiratory depression, subjective discomfort such as nausea may also be harder to acknowledge in a patient with decreased consciousness.

While palliative drugs have known potentially life-shortening adverse effects, typically respiratory depression with the use of opioids and benzodiazepines, (56, 57) and possibly increased mortality with the use of antipsychotics, (58, 59) no life-shortening effect was reported in the studies included in our current review. One study reported a paradoxical prolonging of life as with opioids used for palliative sedation. (38) Similar findings have also been reported with opioids used for dyspnea relief (60) and palliative drug therapy for terminally ill patients in the intensive care unit.(61) The effect has been attributed to the relief from distress. (60)

Strengths and limitations

This review addresses the prevalent and relevant issue of distress in the dying. The review is comprehensive, including seven different databases, and employing broader inclusion criteria than has previously been done, including cohort design studies, and articles in seven languages in addition to English. We employed a rigorous data extraction and quality assessment procedure.

The present review used a clear definition of dying, including individual studies either reporting results in the last two weeks of life, or clinically considered dying. The same cut-off has been used in an earlier review. (5)

Proximity to death naturally engenders high attrition rates in prospective studies, which substantially limited the sample size in several of the included studies. (33, 34, 42) The facts that all studies except one were performed in a palliative care unit or hospital, and almost all patients had cancer, may also limit generalizability to other patient groups and settings. Non-malignant conditions are more prevalent causes of death than cancer. (17, 62) While the relative lack of studies on these patients is representative for palliative care research in general, recent years has seen a shift in the focus toward including non-malignant conditions. (63)

Interpreting symptom outcomes in the included studies must be done with caution for several reasons. The proxy judgement of distress used in many of the included studies, required in

situations where patients lack ability to self-report, is vulnerable to misinterpretation. (15, 64, 65) Patients with dementia, particularly common in the setting of nursing homes, (66) may lack the ability to self-report symptoms long before the dying phase. (67) To complicate this, drugs have multiple effects that treat several symptoms at the same time. In the studies included in this review, midazolam, a primarily sedative drug, is used for symptomatic treatment for several indications such as anxiety, (43) dyspnea, (33, 38, 43) terminal restlessness and refractory symptoms in general. (38) Overlap of symptom presentation and drug effects may make treatment strategies simpler, but complicate the design and interpretation of intervention studies in this population. These and other challenges considered, clinical trials in a more broadly defined end of life care population have nevertheless been shown to be feasible and even to represent a positive experience for patients. (68)

Conclusions

This review found limited evidence regarding the safety and effectiveness of palliative drug therapy for the management of commonly occurring symptoms associated with dying. Current evidence does not support the standard use of anticholinergic drugs in the treatment of death rattle. Some evidence supports the use of morphine and midazolam for dyspnea, anxiety, or terminal restlessness. Limited evidence guides the choice of opioids for pain.

The lack of evidence demonstrated by this review questions our ability to effectively and safely alleviate symptoms in a population that may respond differently to all drug treatments, and yet where patients and family are often reassured with the argument that this can be done. Left with few evidence based options of intervention in the last days and hours of life, efforts to communicate with and prepare patient and family for the likely symptoms of the dying phase become increasingly important. Researchers are particularly urged to include patients with non-malignant disease in clinical trials, and to conduct further high quality clinical trials on pain treatment in the dying.

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Fig. 1 PRISMA diagram of study selection
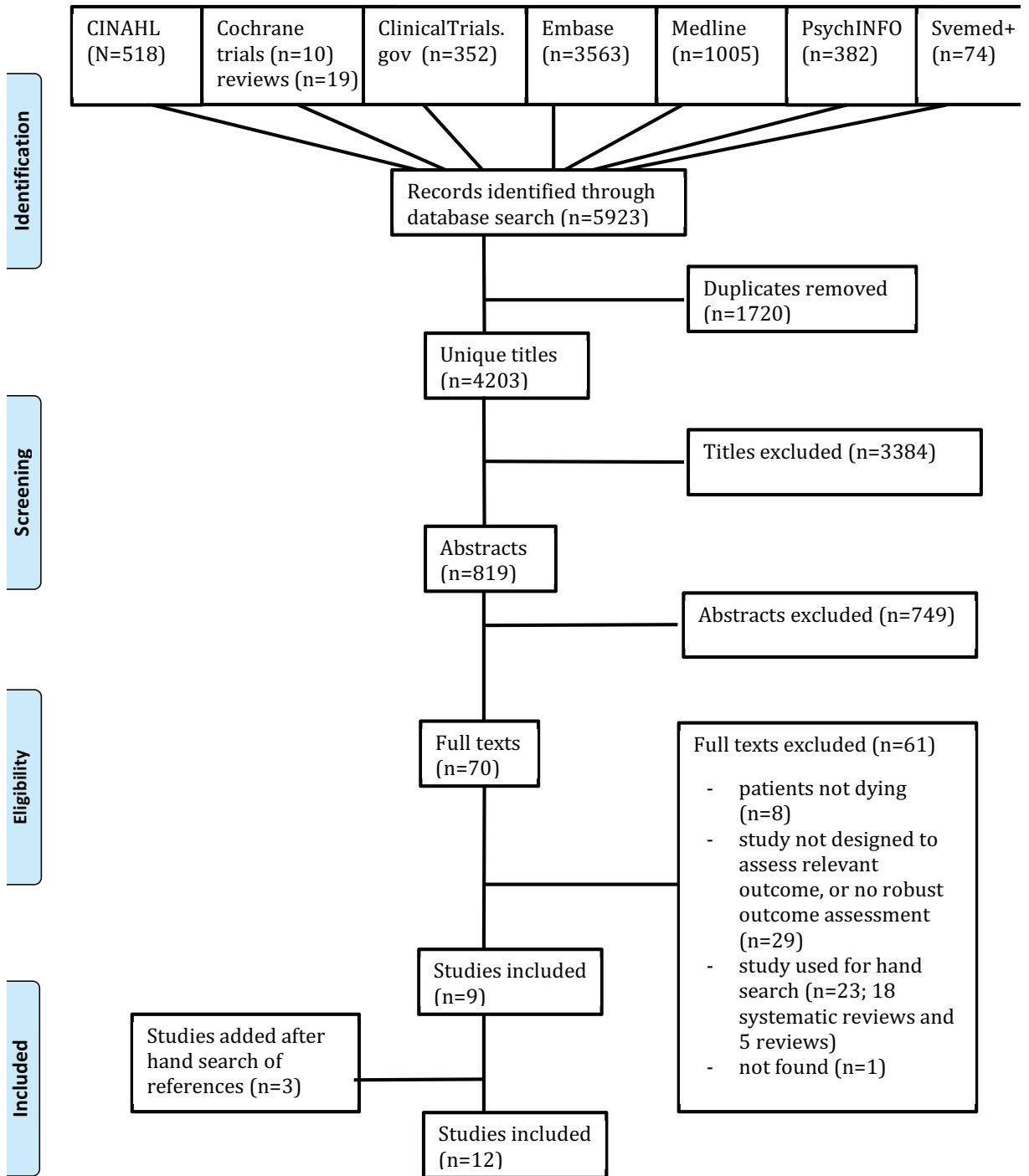
Table I. Characteristics of included studies

First author, Year, Country	Setting	Diagnosis	Time before death studied
Heisler, 2013, USA	PCU	Any (43% cancer)	NR
Likar, 2002, Germany	Hospital Lung dept. Gyn. dept. and Pain Clinic	Cancer	"Terminal" patients
Likar, 2008, Austria/Germany	PCU / Hospital Lung department	Cancer	Life expectancy < 3 weeks
Wildiers, 2009, Belgium	PCU	Cancer (95%)	Median survival 23.9 hours, mean survival 39.2 hours. All died within 350 hours.
Back, 2001, UK	PCU	Cancer (98%)	5 min-5 days from study entry to death
Navigante, 2003, Argentina	Hospital Oncology ward	Cancer	Life expectancy < 1 week
Navigante, 2006, Italy	Cancer Institute	Cancer	Life expectancy < 1 week
Mercadante, 2009, Italy	PCU	Cancer	Median duration of sedation 22 hours (2-160 hours), mean admission time 6.6 days (range 1-15 days)
McIver, 1994, USA	Palliative Care Service inpatients and Hospice Home Care Service outpatients	Cancer	Life expectancy <48 hours, median time patients received chlorpromazine (recorded for 15/20) was 1 day (range l-5)
Pang, 2016, Singapore	Cancer hospital	Cancer	Mean survival from study entry 7 days
Twycross, 1977, UK	Hospice	Cancer	Median survival at unit less than two weeks. About 50% (from Fig.1) of patients died within a week.
Ellershaw, 2002, UK	PCU	Cancer	All patients less than 10 days on the LCP

PCU= Palliative Care Unit   LCP= Liverpool Care Pathway for Care of the Dying Patient   NR= not reported

Table 2. Effective Public Health Practice Project (EPHPP) Quality assessment of included studies

Author, Year	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawal	Global rating
Heisler, 2013	2	1	1	2	2	1	1
Likar, 2002	2	1	1	1	2	3	2
Likar, 2008	2	1	1	1	2	1	2
Wildiers, 2009	2	1	1	3	2	1	2
Back, 2001	2	2	1	2	2	1	1
Navigante, 2003	2	1	1	2	3	1	2
Navigante, 2006	2	1	3	2	1	2	2
Mercadante, 2009	2	2	1	3	2	1	2
McIver, 1994	2	2	3	2	3	2	3
Pang, 2016	2	2	3	3	2	3	3
Twycross, 1977	2	1	1	2	2	3	2
Ellershaw, 2002	2	2	3	2	3	2	3

Component ratings are given as 1=strong, 2=moderate, 3=weak

Table 3. Safety and effectiveness of interventions

First author, Year, Country	Indication	Drug category	Design	Outcome measure	Overall sample size (n)	Intervention	Effectiveness	Safety	Quality[1]
Heisler, 2013, USA	Death rattle	Anticholinergic (atropine)	Double-blind RCT	Reduction of death rattle score by Back (0-3) by ≥1 point, assessed at start, after 2 hours and 4 hours	160	1) Atropine (n=74) 1 mg sublingually (two drops of 1% solution) 2) Placebo (n=63) Two drops of placebo (saline) solution sublingually	No difference between groups Effectiveness after two hours; 38%, 41% (p=0.73) Effectiveness after four hours; 40%, 52% (p=0.21)	No significant difference in heart rate	Strong
Likar, 2002, Germany	Death rattle	Anticholinergic (scopolamine hydrobromide)	Double-blind RCT	Death rattle score (1-5) assessed every 2 hours	31	1) Scopolamine hydrobromide (n=15) 0.5 mg i.v. or s.c. at 0, 4 and 8 hours 2) Placebo (n=16) 1 ml saline solution i.v. or s.c. at 0, 4 and 8 hours	No difference between groups Results presented in figures; percentages and p unknown	NR	Moderate
Likar, 2008, Austria/ Germany	Death rattle	Anticholinergic (scopolamine hydrobromide, glycopyrronium hydrobromide)	Double-blind RCT, pilot	Death rattle score (1-5) assessed every 2 hours	13	1) Scopolamine hydrobromide (n=7) 0.5 mg i.v. at 0, 6 and 12 hours 2) Glycopyrronium bromide (n=6) 0.4 mg i.v. at 0, 6 and 12 hours	Glycopyrronium bromide group responded more often than scopolamine hydrobromide group at 2 hours (p=0.029) and 12 hours (p=0.003). Results presented as figures, percentages unknown	No difference in side effects	Moderate
Wildiers, 2009, Belgium	Death rattle	Anticholinergics (atropine, scopolamine hydrobromide, scopolamine butylbromide)	RCT	Lowering of death rattle score by Back (0-3) to 0 or 1, assessed at start and after 30 minutes, one, four, 12, 24 hours, and then every 24 hours until death. Side effects	333	1) Atropine (n=115) 0.5 mg s.c. bolus, followed by 3 mg/24 hours 2) Scopolamine hydrobromide (n=112) 0.25 mg s.c. bolus, followed by 1.5 mg/24 hours 3) Scopolamine butylbromide (n=106) 20 mg s.c. bolus, followed by 60 mg/24 hours	No difference between groups Effectiveness after one hour; 42%, 37%, and 42% (p=0.72) Effectiveness after 24 hours; 76%, 68%, and 60% (NS; p=NR)	Consciousness decreased more with scopolamine hydrobromide after 12 hours (p=0.0076) but not after 24 hours. No differences in pulse, temperature, and confusion. No difference in survival.	Moderate

[1] Effective Public Health Project (EPHPP), Global rating.
[2] Drug intervention in 42 patients. Survival in this group was compared to 35 additional patients not given the intervention

The names of anticholinergic drugs differ between studies. Both the above table as well as the article text uses the term scopolamine instead of the synonymous hyoscine, and glycopyrronium bromide instead of glycopyrrolate or simply glycopyrronium. Scopolamine exists as two salts with somewhat different pharmacological properties: scopolamine hydrobromide, and scopolamine butylbromide.

s.c. = subcutaneous   i.v. = intravenous   RCT = randomized controlled trial   NS= not significant   NR= not reported   Mo= morphine   Mi=midazolam   MM=morphine plus midazolam   BD= breakthrough dyspnea   VAS=visual analogue scale   RCT=randomized controlled trial   VRS= verbal rating scale

Table 3. Safety and effectiveness of interventions

Study	Symptom	Intervention	Study design	N	Outcome measures	Intervention groups	Results	Side effects	Rating
Back, 2001, UK	Death rattle	Anticholinergics (scopolamine butylbromide, glycopyrronium hydrobromide)	Prospective cohort	170	Death rattle score by Back (0-3) after 30 minutes, 1 hour and last score before death were compared with the initial score and categorized as better, the same, or worse.	1) Scopolamine butylbromide (n=108) 0.4 mg s.c. 2) Glycopyrronium bromide(n=62) 0.2 mg s.c.	Scopolamine hydrobromide gave reduced noise score after 30 minutes compared to glycopyrronium bromide (p=0.002), and less need for a second injection (p=0.03) No significant difference after 1 hour, and on last recorded score.	NR	Strong
Navigante, 2003, Argentina	Dyspnea and anxiety	Opioid (morphine), benzodiazepine (midazolam)	RCT	51	Dyspnea and anxiety intensity (VRS), assessed at start, after 20 minutes and 24 hours. Number of respiratory panic attacks. Nausea and somnolence (0-4)	1) Morphine (n=25) 2.5-5mg/4 hours s.c. plus midazolam (MM group) s.c. 7.5mg if dyspnea score >5 2) Oxygen 4-6L on mask (n=26) 4-6L/min on mask	Improvement in dyspnea for both groups at 20 minutes and 24 hours, MM group better than oxygen at 24 hours (p=0.03) Improvement in anxiety for both groups at 20 min, after 24 hours only in the MM group (p=0.035), MM group better than Oxygen both at 20 minutes (p=0.024) and 24 hours (p=0.032)	Only nausea reported for both groups, 12% in MM group, 15,4% in oxygen group (p=NR), no difference in oxygen saturation (p=NR)	Moderate
Navigante, 2006, Italy	Dyspnea	Opioid (morphine), benzodiazepine (midazolam)	RCT	101	Dyspnea intensity (modified Borg scale) and relief (y/n) assessed every 4 hours. Episodes of breakthrough dyspnea (BD), frequency and severity (1-4) of side effects. Survival	1) Morphine (n=35) 'Mo' 2.5mg/4h continuous s.c., adjusted if baseline opioids, with midazolam rescue doses (5 mg) in case of BD 2) Midazolam (n=33) 'Mi' 5 mg /4 hours continuously s.c. with morphine rescues (2.5 mg) in case of BD 3) Morphine 2.5mg/4h plus midazolam 5mg/4h s.c. (n=33) 'MM', with morphine rescue doses (2.5 mg) in case of BD	Morphine plus midazolam relieved dyspnea significantly better than midazolam and morphine alone at 24 hours (Mo, Mi, MM); 69%, 46%, 92% (MM vs. Mi, p=0.0004; MM vs. Mo, p=0.03), after 48 hours only compared to Mi (p=0.04) Breakthrough dyspnea (Mo, Mi, MM); 34%, 36%, 21% (NS; p=NR)	Group 1) had more cases of distressing side effects (11/17) compared with the other two groups (both 3/17) (p=0.0324), most commonly somnolence. No significant difference in survival (p=NR)	Moderate
Mercadante, 2009, Italy	Dyspnea and terminal restlessness	Benzodiazepine (midazolam)	Prospective cohort	77 (42)[1]	Level of sedation (Communication Capacity Scale, 0-5), assessed every 6 hours. Agitated	1) Midazolam (n=42) Continuous i.v., starting dose around 30-45 mg/day, and then adjusted according to the clinical circumstances	Level of sedation increased (P<0.05), and agitated delirium decreased p=0.0001) with increasing doses of midazolam	Sedated patients survived longer than those not sedated (p=0.003)	Moderate

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Table 3. Safety and effectiveness of interventions

Study	Symptom	Intervention	Design	Outcomes assessed	N	Comparison/regimen	Results	Safety/side effects	Rating
McIver, 1994, USA	Dyspnea and terminal restlessness	Antipsychotic (chlorpromazine)	Prospective cohort, uncontrolled	Level of arousal (1-4), Restlessness (1-4), and Dyspnea alleviation (none/partial/complete) assessed within 24 hours, and then every 24 hours until death; delirium (0-3) at regular intervals. Survival.	20	2) Not on midazolam sedation regimen (n=35); Chlorpromazine (n=20) i.v. (median dose 12,5mg/24hours) or rectally (median dose 25mg/24hours)	Complete symptom relief before death, 18/20. Partial symptom relief, 2/20. Only initial Level of arousal was recorded	NR	Weak
Pang, 2016, Singapore	Dyspnea	Opioid (fentanyl)	Prospective cohort, uncontrolled	Lowering of self-reported dyspnea severity (mild, moderate, severe) after 24 hours compared with at infusion start.	16	Fentanyl (n=16) iv (median dose 7.5 mcg/h in the responder and 12 mcg/h in the nonresponder groups)	No significant difference at 24 hours (nonresponders versus responders = 56.3% vs 43.8%, p=0.33)	Few side effects. Myoclonic jerks or pruritus (1 patient) nausea and vomiting or nightmares (2 patients)	Weak
Twycross, 1977, UK	Pain	Opioids (morphine, diamorphine)	Double-blind crossover RCT	Pain, nausea, mood (100mm VAS) assessed twice daily. Sleep, appetite (100mm VAS), and constipation/need for laxative assessed daily	146	1) Diamorphine hydrochloride, oral (doses NR) 2) equipotent (1:1.5) oral morphine sulphate (doses NR); For both groups, drugs were given in elixir with cocaine hydrochloride 10mg, opioid titrated until pain free. Concurrent antiemetic prochlorperazine or chlorpromazine (doses NR)	Male patients receiving diamorphine experienced more pain (16.8mm difference between group means, p<0.01). No significant difference for female patients	Male patients receiving diamorphine had worse mood score (12.5mm difference, P<0.01) compared to those receiving morphine, while no significant difference for female patients. No difference in constipation and vomiting	Moderate

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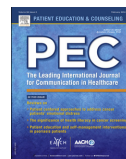
Table 3. Safety and effectiveness of interventions

Ellershaw, 2002, UK	Pain	Opioids (fentanyl, diamorphine)	Retrospective cohort	Total and breakthrough morphine dose, pain control (0-1) assessed every 4 hours	94	1) Fentanyl transdermal patch (n=47) median dose 50mcg/hour 2) Diamorphine syringe driver (n=47) median dose 30mg/24 hours	Both groups had good pain control in the last 48 hours of life. Fentanyl group had higher proportion of patients with controlled pain at 20 (p=0.041) and 8 hours (p=0.002) before death, and fewer 'as required' opioid doses compared to patients in the diamorphine group, the last day of life (p=0.001)	NR	Weak

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III

CrossMark

The impact of existential vulnerability for nursing home doctors in end-of-life care: A focus group study

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A B S T R A C T

Objective: Explore the impact of existential vulnerability for nursing home doctors' experiences with dying patients and their families.
Methods: We conducted a qualitative study based on three focus group interviews with purposive samples of 17 nursing home doctors. The interviews were audio-recorded, transcribed, and analyzed with systematic text condensation.
Results: Nursing home doctors experienced having to balance treatment compromises in order to assist patients' and families' preparation for death, with their sense of professional conduct. This was an arduous process demanding patience and consideration. Existential vulnerability also manifested as powerlessness mastering issues of life and death and families' expectations. Standard phrases could help convey complex messages of uncertainty and graveness. Personal commitment was balanced with protective disengagement on the patient's deathbed, triggering both feelings of wonder and guilt.
Conclusion: Existential vulnerability is experienced as a burden of powerlessness and guilt in difficult treatment compromises and in the need for protective disengagement, but also as a resource in communication and professional coping.
Practice implications: End-of-life care training for nursing home doctors should include self-reflective practice, in particular addressing treatment compromises and professional conduct in the dialogue with patient and next-of-kin.

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1. Introduction

Illness, loss of function, and the prospect of death make all human beings vulnerable to existential suffering. This may include challenges such as dependency, meaninglessness in present life, hopelessness, burden on others, loss of social role functioning, and feeling emotionally irrelevant [1]. Little is known about professional palliative care providers' experiences supporting other people in existential suffering [2]. The doctor's vulnerability is central in Vetlesen's existential approach to the clinical encounter. Acknowledging vulnerability as a basic element of humanity common to both patient and doctor, he argues, is a precondition for accessing the patient's perspective [3]. Although intuitively viewed as a weakness, the doctor's vulnerability may be valuable

to successful patient communication [3,4]. Doctors' own existential vulnerability facing matters of life and death has been underestimated [5], and it is unclear how such vulnerability should be viewed as part of a professional identity.

Kissane suggests eight types of existential challenges for patients with advanced illness: 1) death anxiety, 2) loss and change, 3) freedom with choice, 4) dignity of the self, 5) fundamental aloneness, 6) altered quality of relationships, 7) meaning, and 8) mystery [6]. To each of these, he offers a suggestion to doctors on how to facilitate adaptive responses. Kissane's typology might also be useful to understand the challenges of doctors working in EOL care, given the common human nature of patients and doctors. However, the doctor's professional role is defined as a contrast to the patient role, thereby potentially also alienating itself from the vulnerability of its counterpart. Such an opposition may have consequences for the experiences and expressions of existential distress, adaptive responses, and facilitation strategies for doctors.

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About 45% of deaths in Norway occur in nursing homes [7], making them the most common provider of end-of-life (EOL) care in the country. Nursing home doctors are central team-members in EOL care responsible for treatment decisions such as initiation and withdrawal of drug therapy, and hospital admission. These decisions are often difficult. Nursing home doctors value a well-functioning relationship with the nurse [8]. They also value consensus about the patient's health status and an appropriate care plan between staff, as well as with the patient and family [9]. They perceive themselves to provide less emotional support to families compared to nurses and aides [10], and family members call for their increased involvement in EOL care [11,12]. Discordance between the demand from staff for medications and the patients' actual need of nursing care is reported, in particular when not being able to fulfill the existential needs of the nursing home patients [8].

As experienced nursing home doctors, GPs (KJ and SR), and a hospital doctor (MAS) with a key interest in improving EOL care, and studying existential conversations and interactions (KM and MAS), we therefore set out to explore the impact of existential vulnerability for nursing home doctors' experiences with dying patients and their families.

2. Methods

We conducted a qualitative study based on three focus group interviews, each including five to six nursing home doctors, conducted in two Norwegian municipalities.

2.1. Study context and participants

Norway spends a higher share of total health expenditures in long-term care facilities than most countries in the world [13]. In 2014, doctors were available on average 0.49 weekly hours per nursing home bed [14]. Nursing home doctors in Norway are a blend of general practitioners providing a part-time service, and increasingly, dedicated nursing home doctors commonly working at larger nursing homes.

Participants were recruited by email correspondence, with senior consultants in the municipalities providing contact information. The first focus group was invited directly by email to the nursing home doctors. In further recruitment this approach did not prove fruitful. Local groups of nursing home doctors meeting for Continuing Medical Education purposes therefore provided starting points for recruitment for the last groups.

We included a purposive sample of 17 nursing home doctors based in two Norwegian municipalities, aiming for variation in gender (10 women, 7 men), age (33–65 years), clinical experience (3–29 years), part-time or full-time engagement (14 versus 3), and specialty background (3 doctors were specialists in general practice, 3 hospital specialists, the remainder had no specialty background). The first author knew several participants in the first and second focus groups from earlier work as a nursing home doctor in the same municipality. Most doctors did not declare any particular religious background, seven doctors declared a Christian faith, and two described themselves as agnostic.

2.2. Data collection

The moderator (KJ) asked participants to share an episode treating seriously ill or dying nursing home patients that they found challenging. After the first interview, in an attempt to facilitate stories of vulnerability or challenges while also allowing for stories of success, participants were invited to share an experience that had made a profound impression on them. These stories were starting points for an open exploration of participant's experiences, using a brief interview guide covering issues such as prognostication, own relationship to death, and talking about dying.

The interviews lasted for 90 min. The first author served as moderator in all interviews, the last author as secretary taking field notes. The first author taped and transcribed the interviews verbatim. Data collection was closed after three focus group interviews, as we assessed the data sufficiently rich to illuminate the research question.

2.3. Analysis

All authors participated in the analytical process following the steps according to Systematic Text Condensation [15] (Fig. A1) [16]. First, we read the transcripts for an overall impression, identifying preliminary themes. Second, units of meaning were identified and coded independently by all the authors, representing different aspects of challenging experiences in EOL care and how these were dealt with. Third, the content of the code groups and subgroups was abstracted into condensates, each illustrated by a quotation. Fourth, generalized descriptions of experiences with dying patients associated with existential vulnerability were developed in an iterative process. Theoretical perspectives from Kissane [6] and Vetlesen [3,17] sharpened the interpretative focus [18] of the final analytic stages on experiences concerning existential vulnerability. At each step, the code groups were reflected upon and renegotiated in the author group. A decision trail documented the choices during the analytic process [19].

2.4. Ethics and approval

The Western Regional Committee for Medical and Health Research Ethics (2012/1091) and Norwegian Social Science Data Services (#31098) approved the study. Pseudonym participant names were used in the transcription and analysis.

3. Results

Nursing home doctors experienced having to balance treatment compromises in order to assist patients' and families' preparation for death, with their sense of professional conduct. This was an arduous process demanding patience and consideration. Existential vulnerability also manifested as powerlessness mastering issues of life and death and families' expectations. Standard phrases could help convey complex messages of uncertainty and graveness. Personal commitment was balanced with protective disengagement on the patient's deathbed, triggering both feelings of wonder and guilt. These findings are elaborated below. Selected quotations have been chosen to illustrate the findings.

3.1. Doctors balance treatment compromises in order to assist patients' and families' preparation for death, with their sense of professional conduct

The doctors unanimously emphasized the importance of preparing patients and their families for death. They described advance care dialogues, grief work and joint decision-making in many occasions to be a slow and arduous process for all parties. They experienced a duty to take into account the requests of next-of-kin in decision-making, as these would later have to live with the consequences. Doctors sensed that family members needed to see the patient be given "a chance" to realize that the patient's life could not be saved. Accepting futile treatment in order to ease the grief process for the next-of-kin could oppose the patient's wishes as well as the doctors' professional standards. In such situations, doctors felt the need for difficult compromises, revealing and

challenging their own vulnerability. These compromises included administering intravenous fluids, nutrition and antibiotics in discord with the doctors' professional and personal opinion. An experienced doctor described how he yielded to pressure from relatives for further treatment, in a patient with metastasized lung cancer who did not want treatment:

«*And then there came a moment when the family and his wife said: yes, but isn't he going to get nutrition? And at that point nutrition wasn't medically relevant, but just to do something good. (. . .) And I did go so far, then, that I ordered intravenous nutrition. (. . .) I have many times been in situations where . . . we actually have to yield quite a lot.*» (Nathan)

The participants said that it was essential to them to adopt an attitude of patience and carefulness in these challenging processes. They would encounter widely different patients and families, with varying degrees of acceptance of their situation, need for information and preparedness for death. Doctors described treading gingerly, sometimes taking a step back, listening and not pushing things. One doctor told about his negotiations with the family of a seriously ill stroke patient who repeatedly pulled out his feeding tube. It took many conversations with the whole family before they accepted not giving the patient yet another feeding tube. Another doctor had a similar story regarding intravenous drips:

«*What makes this so hard? I think it's . . . We see that we can't do what's best for the patient, what we think is the best for the patient, and what the patient says that he wants. (. . .) And that I think is quite a difficult ethical dilemma.*» (Sarah)

3.2. Doctors' vulnerability manifested as feelings of powerlessness mastering life and death, and families' expectations

Several participants described situations where they felt powerless and uncertain in their professional role. This could be with patients that were difficult to palliate, striving to find words to console the patient or families, or when they could not uphold their assurances to the patient or families. A young nursing home doctor spoke of her meeting with an old patient with grave and deteriorating heart failure. She was overwhelmed by the task of both having to console both the patient and her family:

«*I was unsure if she was dying, if she knew who was around her, and if she could hear anything at all. Then I spoke to her, while her daughter was crying, and I felt that I fell short of helping both of them. I tried speaking to the patient, the dying woman, but didn't know what to say to the daughter. It was hard. I couldn't find any comforting words.*» (Trish)

Another challenge for the doctors was to respond to patients' or next-of-kin's inquiries about prognosis, reflecting an uncertainty regarding diagnosing dying patients. They feared a «Lazarus-effect», whereby the patient suddenly would improve after having removed their regular medications and their families having been informed of imminent death. To deal with this, the doctors employed standard wording that would convey the seriousness of the situation and at the same time the uncertainty, such as: «I have stopped guessing», «this is no longer in our hands», or «we will let nature take its course». They would seldom use religious allusions, but a doctor who himself was not Christian would sometimes say «God has a plan with us all». Even in the cases where death was clearly near, the doctor could feel guilty of being the «bad informer» explicitly revealing the patient her dire prognosis. An experienced female doctor speaking to a patient with senile dementia illustrated this vulnerability:

«*And we knew he would die. And we had agreed that if he asked, I would be the bad guy informing him, and the nurse would comfort him. (. . .) But then he lay there in bed, breathing heavily, and then he says to me, because he knew I was a doctor: 'Out of breath'. I say: 'Yes,*

you are ill'. Then he looks at me and says: 'is it serious?' And I answer 'Yes.' And then he asks: 'Will I die?'. And he had dementia, and it was a little difficult to answer straight out 'Yes' to that. I felt. (. . .) I answered: 'Yes', and then I had a little break, and then I said: 'We are all going to die'. (Mary)

3.3. Balancing personal commitment and protective disengagement on the patient's deathbed

Several participants expressed their own acquaintance with death as difficult. Conversations about death at the ward were demanding, and they would often hesitate to engage in them. They said that the death of a patient could remind them of the eventuality of their own parents or children falling in a similar situation. A male doctor felt guilty about not showing as much feeling as the nurses would after his patients had passed away, even though he had participated in several patients' funerals. He interpreted this as self-protection against personal involvement, similar to when he sometimes referred to the local vicar service instead of himself talking with the patient about death. Several participants experienced seemingly contradictory feelings, as they witnessed the end of a prolonged trajectory of suffering – a feeling of compassion could alternate with, or change into, relief:

«*I remember once, to see them not have to suffer any more, for example to see them the next day lying nicely cleaned in bed . . . There was a sailor here who died, he had a terrible last year after a stroke, and suddenly he lay in bed completely relaxed, with seagulls crying in the background – because they always have seagulls and baby seagulls here in the summer – it was incredible! There's something about it, that it can be good to let go, and in a way have a peace about it.*» (Elisabeth)

The doctors expressed that by daring to take off their white coat and making themselves accessible as fellow human beings, time spent with the dying and their relatives could feel sacred, meaningful and rewarding. Several participants described touching encounters with patient and families. A dying patient with dementia would in a clear moment share a dream of her deceased husband with the doctor. The doctors described a sense of awe to sit by the patient deathbed, holding the dying person's hand, and feeling a peace and calm unique to dying. They sometimes felt deep gratitude in patients when futile treatments were abandoned, and were happy when they managed to comfort patients by talking and not only prescribing medications. The joy of seeing the patient as a person and not just for their illness also gave a greater perspective on their own lives, and an opportunity to cope better in a difficult profession, some of them remarked. A young doctor expressed how daring to be a buddy with an alcoholic patient with liver cancer in his last two months had facilitated their interaction when the day came that the patient was dying, and words were more difficult to find.

«*He was not one of those I followed for years. However, in a way it was hard for me not being able to contribute so much. Just being present. But on the other hand . . . with him I didn't have to say so much. He recognized me when I came in. And we were both at ease with the fact that he had complaints that we could not fully palliate. And that things were going downward. I felt that was something positive, too.*» (Gary)

4. Discussion and conclusion

4.1. Discussion

Feeling at times powerless before the palliative and communicative challenges surrounding death, doctors balance both personal commitment with protective distance, as well as treatment compromises with their sense of professional conduct,

in an arduous, integrated process of decision-making and grief work. Below, we discuss strengths, limitations, and interpretations of these findings.

4.1.1. Validity and transferability

Focus-group interviews are preferable in seeking information on attitudes, viewpoints, and personal experiences in environments of cooperation and interaction [20,21]. Even though exposing vulnerability of the participants could have called for the more intimate setting of individual interviews, the group seemed well able to admit shortcomings and share challenging experiences, successful or not. We believe that the participants, facilitated by group reflection, were presenting their experiences without excessive concern about making a favorable impression. Contributing to this may have been the fact that most of the participants knew each other [22,23], and all including the moderator and secretary shared the same profession, as well as familiarity dealing with life-and-death issues. The fact that the first author knew several of the participants in the first and second focus groups, may also have contributed to this. However, we did not notice any substantial difference in the ease of discussion nor subjects raised between the groups. The purposive sample of participants represented a rich variation in age, gender, working experience, and nursing home institutions. Although EOL care is a team effort, our study focused on nursing home doctors, as compared to other staff groups or care providers. This is because factors considered important at the end of life are known to differ by professional role [24]. Also, we consider the voice of nursing home doctors faint in previous literature, and their existential vulnerability an underexposed issue.

Although we believe international comparisons to our results are reasonable within a Western cultural setting, doctor's experiences are likely to be influenced by factors such as doctor availability and EOL care competence, role of nursing home in health care, and cultural differences in attitudes and communication. In particular, doctor availability and staff resources are likely to allow more time for patient and family dialogue, as well as the reflection and self-care that have been shown central to coping with the emotional, physical, and existential demands of EOL care [25–28]. Norway's health expenditures in long-term care facilities are privileged in a global perspective, comparable mainly to the Netherlands, Switzerland, Belgium, Denmark, and Sweden [13].

The authors' preconceptions are an integral element of interpretation in qualitative studies. The nature of EOL care as burdensome yet rewarding was part of the authors' preconceptions from own experience. Nursing home medicine and EOL care have low-status in healthcare. As a nursing home doctor and general practitioner, the first author has firsthand experience of a complexity and sense of importance to this work that feels to deserve otherwise. We may therefore have had a special awareness for aspects of EOL care that are personally and professionally challenging yet rewarding.

4.1.2. Doctors' existential vulnerability – what does this study add?

Our study adds to existing knowledge by presenting the concrete impact of existential vulnerability in the context of nursing home doctors working in EOL care, such as how they balance personal commitment with protective distance, and professional conduct with treatment compromises. Furthermore, our analysis adds to the understanding of nursing home doctors' experiences in EOL care, where emotions such as powerlessness and guilt, and strategies such as standard phrasing, are further interpreted in an existential context below.

In Kissane's existential typology, the perceived powerlessness of doctors facing the dying patient may be viewed as a threat to their need of control, and in prolongation, to their professional freedom and autonomy [6]. Nursing home doctors positively value freedom and autonomy [8,25]. The need to know the timing of death nevertheless seems more important to patients and family than doctors [29]. Standard expressions of uncertainty of prognosis, such as "we will let nature take its course" may help situate the doctor on the side as an onlooker, a position that relieves their responsibility for the ensuing course of illness. Our analysis demonstrated how protective disengagement from the situation of dying could be balanced by experiences of personal presence and a sense of awe. Such a feeling of reverence for the mystery of death, points to the spiritual significance of EOL care. The adaptive responses of doctors here swing between peaceful presence and guilt-laden distance, illustrating that professional conduct in this specific context is not straightforward.

In long-term care doctors may know patients for months or years. This could make doctors feel closer to and more easily be vulnerable in front of their patients, or more easily be touched. Nevertheless the story of being a devil's advocate of an explicit message of death that nobody wants to be associated with, demonstrates the stigma of death, and the doctor's instinct to preserve dignity for herself and her patient. The doctor may fear removing hope, adding to the burden of the patient, or making the prognosis self-fulfilling [29]. Participants also felt guilty for not showing feelings before the patients and their families, at the same time needing a protective distance. A need for emotional control is clearly not unique to doctors relating to dying patients or their families. In view of Kissane's perspectives, however, a need for distancing from death and dying is also an expression of human beings' anxiety of death [6].

Doctors' vulnerability may on the other hand be more linked to their sense of responsibility than to death itself, consistent with what has been shown in interviews with hospital doctors [5]. Sharing responsibility helped these doctors create a supporting alliance with their patients similar to the joint decision-making processes and compromises with patient and next-of-kin described by our participants. Our findings support Aase Schaufel's idea of a "vulnerable responsibility" of nursing home doctors in EOL care [5]. This is demonstrated by the difficult balance of treatment negotiations with next-of-kin, and the doctors' sense of professional conduct. The powerlessness experienced by the doctors may in part also be viewed as a consequence of assuming a vulnerable responsibility for the challenging, and one must assume often unsuccessful, task of palliating existential suffering. While there is a broad range of manualized interventions for treating existential distress in patients [30], limited empirical research exists on the effectiveness of these [26].

A central concern for medical professionalism is patient welfare [31,32]. In contrast, participants told many stories of next-of-kin centered decision-making. Next-of-kin are important proxy responders in EOL decision-making. Many barriers have been reported to proxy decision-making for people with dementia, and end of life decisions are considered particularly difficult to make as such [33]. The views of cognitively able nursing home patients and their relatives have been reported to differ [34]. Although the insistence of patient and family on interventions that the doctor considers futile is not a surprise [35], treatment decisions possibly aggravating the suffering of the dying patient raise important questions of ethical focus and legal acceptability. Doctors would not be vulnerable to this dilemma had they not experienced a conflicting moral obligation of beneficence and non-maleficence [36] toward next-of-kin.

Showing emotions and personal commitment may be commensurable with professionalism to the extent that it reflects respect for the patient and next-of-kin, and does not hamper good judgment [32]. As exposed by Vetlesen [3] and further elaborated in later studies [4,5], doctors in the present study express how
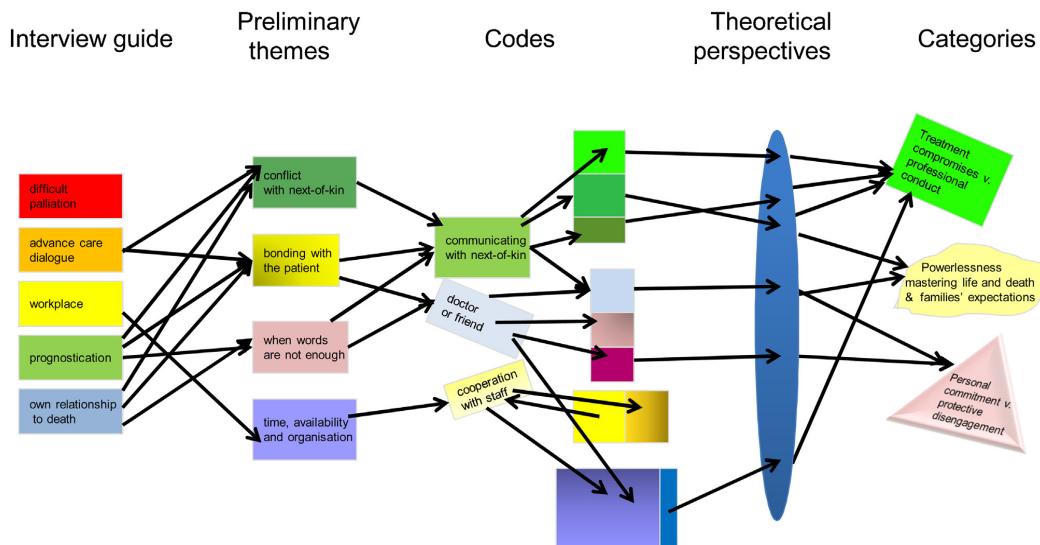
Fig. A1. Analytic process. The figure illustrates keywords in development of categories, as well as the non-linearity of the analytic process. Codes are malleable and vary in the course of analysis. Theoretical perspectives from Kissane and Vetlesen were used as a lens through which interpretation was focused on the existential aspects of the participants' experiences. Modified with permission after [16]: Malterud K. Kvalitative metoder i medisinsk forskning. [Qualitative methods in medical research] 3rd ed. Oslo: Universitetsforlaget; 2011.

compassionate engagement and revealing a shared human vulnerability may even be desirable in strengthening the partnership with patient and next-of-kin.

4.2. Conclusion

Existential vulnerability in the experiences of nursing home doctors working in EOL care is on one hand encountered as a burden. This is shown in feelings of powerlessness and guilt facing prognostic and palliative challenges, the difficult balance of treatment compromises with next-of-kin with professional conduct, and the occasional need for protective disengagement from difficult situations. Powerlessness may be enhanced by the doctors' own need for control. The shared human anxiety for death, the stigma of death, and doctors' sense of responsibility contribute to vulnerability. On the other hand, existential vulnerability is also experienced as a resource in communication and professional coping, by allowing for meaningful experiences.

4.3. Practice implications

Existential vulnerability plays an important role in understanding EOL care communication and in furthering professional self-care and reflection. Professional conduct in EOL care is not straightforward but needs to take into consideration both the doctor's vulnerability as well as that of the patient and next-of-kin. EOL care training for nursing home doctors may benefit from including self-reflective practice, and in particular address treatment compromises and professional conduct in the EOL dialogue with patient and next-of-kin.

Conflicts of interest

None declared.

Appendix A.

See Fig. A1.

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Appendix 1

Systematic literature review

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

        1 Very likely
        2 Somewhat likely
        3 Not likely
        4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

        1 80 - 100% agreement
        2 60 – 79% agreement
        3 less than 60% agreement
        4 Not applicable
        5 Can't tell

RATING SECTION A   Strong=1 Moderate=2 Weak=3

B) STUDY DESIGN

Indicate the study design:

        1 Randomized controlled trial
        2 Controlled clinical trial
        3 Cohort analytic (two group pre + post)
        4 Case-control
        5 Cohort (one group pre + post (before and after))
        6 Interrupted time series
        7 Other specify _____
        8 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATING SECTION B   Strong=1 Moderate=2 Weak=3

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?

    1 Yes

2 No

3 Can't tell

The following are examples of confounders:

1 Race

2 Sex

3 Marital status/family

4 Age

5 SES (income or class)

6 Education

7 Health status

8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?

1 80 – 100% (most)

2 60 – 79% (some)

3 Less than 60% (few or none)

4 Can't Tell

RATING SECTION C	Strong=1 Moderate=2 Weak=3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1 Yes

2 No

3 Can't tell

(Q2) Were the study participants aware of the research question?

1 Yes

2 No

3 Can't tell

RATING SECTION D	Strong=1 Moderate=2 Weak=3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?

1 Yes

2 No

3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes

2 No

3 Can't tell

F) WITHDRAWALS AND DROP-OUTS

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

        1 Yes
        2 No
        3 Can't tell
        4 Not Applicable (i.e. one time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study.
 (If it differs by groups, record the lowest).

        1 80 -100%
        2 60-79%
        3 less than 60%
        4 Can't tell
        5 Not Applicable (i.e. Retrospective case-control)

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

        1 80 -100%
        2 60-79%
        3 less than 60%
        4 Can't tell

 (Q2) Was the consistency of the intervention measured?

H) ANALYSES

(Q1) Indicate the unit of allocation   (community organization/institution practice/office individua

(Q2) Indicate the unit of analysis (community organization/institution practice/office individual)

(Q3) Is it likely that subjects received an unintended intervention that may influence the results

Yes No Can't tell

Yes No Can't tell

(Q3) Are the statistical methods appropriate for the study design?

 1 Yes
 2 No
 3 Can't tell

(Q4) Is the analysis performed by intervention allocation status rather than the

actual intervention received?
  1 Yes
  2 No
  3 Can't tell

GLOBAL RATING COMPONENT RATINGS

A) SELECTION BIAS		
B) STUDY DESIGN		
C) CONFOUNDERS		
D) BLINDING		
E) DATA COLLECTION METHOD		
F) WITHDRAWALS AND DROPOUTS		
GLOBAL RATING FOR THIS PAPER:		

1 = STRONG   No weak ratings
2 = MODERATE   One weak rating
3 = WEAK   Two or more weak ratings

With both reviewers discussing the ratings:
(no WEAK ratings) (one WEAK rating) (two or more WEAK ratings)
Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings? No Y
If yes, indicate the reason for the discrepancy
  1 Oversight
  2 Differences in interpretation of criteria
  3 Differences in interpretation of study

Final decision of both reviewers :

SYSTEMATIC LITERATURE REVIEW: Search strategy

Database: Embase (Ovid)

Final search date: 21. December 2016

1   death/ or dying/ (366263)
2   terminally ill patient/ or hospice patient/ (8793)
3   terminal care/ or hospice care/ (36872)
4   palliative therapy/ or cancer palliative therapy/ (92150)
5   (dying or die* or death).ti,kw. (396362)
6   ((terminal or palliati*) adj1 care).ti,kw. (21516)
7   "terminally ill".ti,kw. (2158)
8   "terminal illness".ti,kw. (583)
9   (palliati* adj1 stage*).ti,ab. (600)
10   ("end of life" adj2 (stage or stages)).ti,ab. (113)
11   or/1-10 (819616)
12   "end of life".ti,ab. (21783)
13   ((last or final) adj1 (hour* or day* or minute* or stage* or week* or month*)).ti,ab. (26216)
14   ((dying or terminal) adj1 phase*).ti,ab. (2747)
15   ((dying or terminal or end) adj1 stage*).ti,ab. (79293)
16   (dying adj2 (actively or begin* or begun)).ti,ab. (98)
17   (death adj2 (imminent* or impending or near or throes)).ti,ab. (2163)
18   ((dying or death) adj2 (patient* or person* or people)).ti,ab. (32402)
19   (Body adj2 (shut down or shutting down or deteriorat*)).ti,ab. (165)
20   (deathbed or death-bed).ti,ab. (132)
21   or/12-20 (158358)
22   11 and 21 (47067)
23   drug therapy/ or diuretic therapy/ or drug combination/ (662242)
24   prescription/ (161366)
25   exp anxiolytic agent/ (182812)
26   exp neuroleptic agent/ (250013)
27   exp benzodiazepine derivative/ (169759)
28   exp antiemetic agent/ (172497)
29   exp cholinergic receptor blocking agent/ (168289)
30   exp diuretic agent/ (333178)
31   (morphin* or opioid*).ti,ab,kw. (132265)
32   (anti-anxiety agent* or Midazolam or anxiolytic* or diazepam or oxazepam or lorazepam or benzodiazepine*).ti,ab,kw. (88944)
33   (antiemetic* or antipsychotic* or haldol or risperidone).ti,ab,kw. (63970)
34   (anticholinergic* or anti-cholinergic* or glycopyrronium or scopolamine or hyoscine).ti,ab,kw. (25128)
35   (diuretic* or furosemide).ti,ab,kw. (58694)
36   or/23-35 (1717194)
37   22 and 36 (4600)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5, Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12-13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, Table 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-9, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

For more information, visit: **www.prisma-statement.org**.

Appendix 2

Focus group study

uni Helse
Allmennmedisinsk forskningsenhet
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Helsepersonells utfordringer i møte med døende sykehjemspasienter

Forespørsel om deltagelse - til deg som er helsepersonell på sykehjem i Bergen:

Vi ønsker med dette å informere deg om et forskningsprosjekt som foregår på sykehjem i Bergen Kommune. I forbindelse med dette søker vi helsepersonell som vil delta på et gruppeintervju.

Studien består av gruppeintervjuer med henholdsvis leger, sykepleiere, og helsefagarbeidere. Vi skal undersøke hvilke utfordringer helsepersonell opplever når de har ansvar for døende pasienter på sykehjem. Målet er å prøve å bidra til bedre ivaretakelse av pasienter og pårørende ved livets slutt, og avdekke tiltak som gjør helsepersonell bedre rustet til å møte de utfordringene som behandling av døende innebærer.

Studien utgår fra Allmennmedisinsk forskningsenhet (Uni Research), er finansiert av Den norske legeforeningen, og vil gå over tidsrommet 2012 -2013. Prosjektleder er prof.dr.med. Sabine Ruths, og medveileder er forsker og lege Margrethe Aase Schaufel. Studien er meldt til Regional etisk komité for medisinsk forskning (REK Vest), samt Norsk Samfunnsvitenskapelig Datatjeneste (NSD).

Alle personopplysninger vil bli behandlet konfidensielt, slik at man ikke kan gjenkjennes i presentasjonen av forskningsresultatene. Det er fullt mulig å trekke seg underveis, til dess datamaterialet er anonymisert 31/12-2013. Det er ingen økonomisk kompensasjon for deltakelsen. Skulle det oppstå ubehagelige opplevelser ved deltakelsen, vil vi legge til rette for best mulig oppfølging.

Dersom du ønsker å delta etter å ha lest denne informasjonen, vil vi be deg signere samtykkeerklæringen som er vedlagt og levere til ledelsen ved sykehjemmet. Ta kontakt ved spørsmål på tlf 94501822, eller epost: jansen.kristian@gmail.com. Tusen takk for hjelpen.

Vennlig hilsen   Bergen, juni 2012

Kristian Jansen (forsker)   Sabine Ruths (prosjektleder)

Uni Helse er en avdeling i forskningsselskapet Uni Research.
Avdelingen utfører og formidler forskning innen fagområder som har betydning for helse, livsstil og arbeid.

Uni Health is a department of the research company Uni Research.
The department conducts and disseminates research in specialist fields relating to health, lifestyle and work.