Continuous palliative sedation:

determinants, practice and outcome

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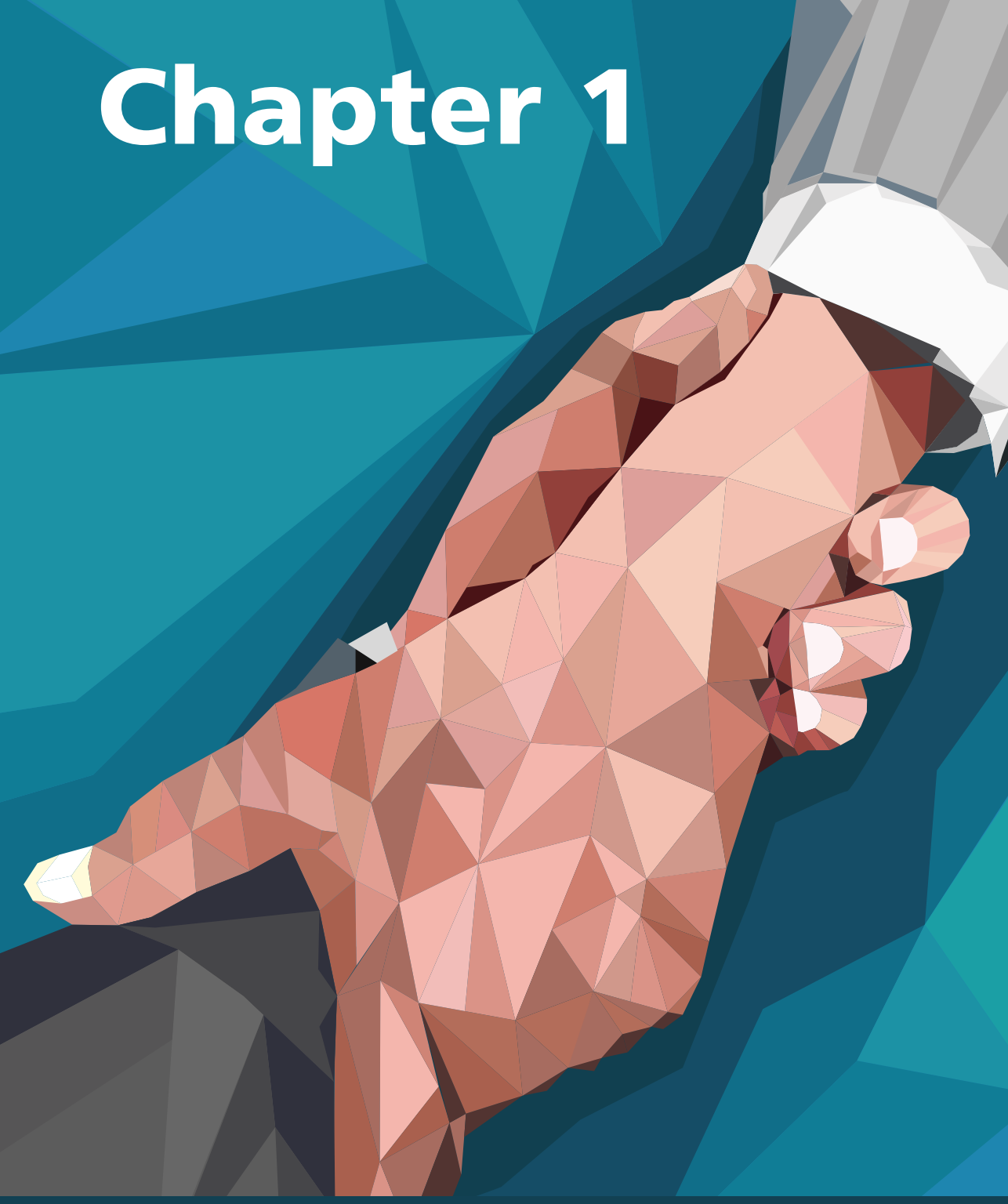
'Koude handen, warme gevoelens'

Ter nagedachtenis aan mijn vader

Chapter 1



Introduction

Chapter 1

Introduction

Palliative care

A century ago, death was typically quite sudden, and the leading causes were infections, accidents, and childbirth.[1,2] At that time, a healthy person who became sick either recovered or died, and there was no medical involvement or any medical involvement lasted only for a very short period of time.[2] Today, due to improved public health and medical treatments, the overall trend worldwide is towards increasing longevity, with ageing of populations as one of its consequences.[1-3] As a result, sudden death is less common, and more chronic diseases such as cancer, dementia and chronic organ failure shape the last years of life for a large part of the population.[2] In the Netherlands, the annual absolute number of deaths for the last decade was 136 724.[4] Six out of ten of these deaths were preceded by end-of-life decisions, such as intensive symptom control and withholding or withdrawal of medical interventions, and in one out of four of these deaths, an elderly care physician, formerly called nursing home physician, was the attending physician.[5,6] The primary aim of the care in the last phase of life of these often older patients is to optimize quality of life, which is the basic philosophy of palliative care.[1] Palliative care is defined by the World Health Organization 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. Palliative care provides relief from pain and other distressing symptoms; affirms life and regards dying as a normal process; intends neither to hasten or postpone death; integrates the psychological and spiritual aspects of patient care; offers a support system to help patients live as actively as possible until death; offers a support system to help the family cope during the patients illness and in their own bereavement; uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated; will enhance quality of life, and may also positively influence the course of illness; is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications."[7]

Palliative care for the needs of a patient with an incurable disease has to be viewed as a continuum of care, starting at diagnosis and with death as the end-point.[2] At the end of this continuum of palliative care, palliative sedation can be administered as a medical intervention.[8,9]

Palliative sedation

If one or more symptoms in a dying patient cause unbearable suffering and conventional modes of treatment are not effective or fast-acting enough and/or if these modes of treatment are accompanied by unacceptable side-effects (so-called refractory symptoms), an indication arises to administer palliative sedation.[10-13] Palliative sedation is defined as "the deliberate lowering of a patient's level of consciousness in the last stages of life."[10] The objective of palliative sedation is to alleviate the patient's discomfort caused by refractory symptoms.[10-13] Palliative sedation should be applied proportionately; the dose of sedative should be individually titrated.[10-13] The term "palliative sedation" encompasses two distinct types of intervention: brief or intermittent sedation and continuous sedation administered until death (CPS).[10] Although both interventions represent stages in the ongoing process of providing proportional sedation for refractory symptoms, the distinction is made to emphasize the fact that CPS is only to be administered to patients who are near death.[10]

CPS is considered as a last resort intervention; it not only takes away a patient's suffering until the moment of death but also produces an impaired capacity to communicate.[8,9] Hence, potential positive and meaningful experiences a patient might have are taking away, such as pleasant moments shared with family, communication, and the ability to reflect upon himself.[13-18] In addition, research shows that relatives, nurses and physicians sometimes experience the administration of CPS as a burden.[19-22] Relatives expressed concerns regarding sedation in approximately half of the cancer patients for whom CPS was used in an acute palliative care unit.[20] These concerns could be classified into three main themes: concerns about the aim of CPS, concerns related to the well-being of the patient, and concerns related to the well-being of the relatives themselves. Moreover, relatives reported that they were distressed about the inability to communicate with a patient.[22] Physicians reported, more often than nurses, that they felt they were put under pressure to start continuous sedation, mostly by patients and relatives.[19,21]

Palliative sedation in the literature

In 1990, Ventafridda and colleagues were one of the first to describe sedation at the end of life in relation to uncontrollable symptoms in terminal cancer patients and noted that more than 50% of these patients died under sedation.[23] In 1991, Enck introduced the term "terminal sedation" into the literature.[24] Enck did not specifically define "terminal sedation" but presented studies showing that some patients dying with cancer had unrelieved suffering in their final days and that providing medication to relieve this suffering could only be accomplished by reducing their consciousness.[25] In the following years, an increase in the number of empirical studies on this topic were carried out, and terminal sedation was substituted in the majority of the studies by the term palliative sedation.[26] Recently, a Cochrane review was performed to assess the evidence for the benefit of palliative sedation on quality of life, survival and specific refractory symptoms in terminally ill adults during their last few days of life.[27] This review included 14 studies with a total of 4167 adults, of whom 1137 received palliative sedation. The proportion of people in each study receiving palliative sedation ranged from 12% to 67%. In all the studies, the proportion of people with a cancer diagnosis was greater than 95%. The settings of these studies were hospices, palliative care units, hospital oncology wards, and home-based palliative care; three studies involved more than one setting. The most common indications for palliative sedation were delirium, dyspnea, pain, existential distress, anxiety, and mental anguish. The most commonly used drug to achieve palliative sedation was midazolam, and the mean duration of sedation from initiation to death ranged from 19 hours to 3.4 days. Other reviews on palliative sedation report similar findings with respect to indication, duration and medication.[13,26,28-31] All these reviews emphasize the significant lack of research in this area and the need for more clinical, prospective and multicenter research on topics such as the efficacy, establishing proper instruments for monitoring, the most adequate frequency and timing of assessment, and the interdisciplinary evaluation of sedation depth and symptom control.[13,26,27-31]

Palliative sedation in the Netherlands

In the Netherlands, one of the first publications on sedation at the end of life was published in 1998 in the Dutch Journal of Medicine (NTVG).[32] The authors described four terminal cancer patients with terminal restlessness, emphasizing that interventions directed at problems such as withdrawal symptoms, metabolic derangements, urinary and/or faecal retention and intoxication by drugs should be considered before starting sedation. A year later in the same journal, the importance of

timely assessment of the patient's preference for end-of-life interventions was brought to attention, and a distinction was made between sedation at the end of life and euthanasia, arguing that sedation does not shorten life.[33] In 2002 and 2003, practice guidelines for sedation at the end of life, released by two Comprehensive Cancer Centers, underlined the distinction between sedation and euthanasia and described the indication and administration of sedation.[34,35] Despite these regional guidelines, controversies regarding the clinical practice of sedation arose. These controversies were illustrated in 2003, when a Dutch anaesthesiologist administered morphine and midazolam to a suffocating terminal patient. After he reported a natural death, he was accused of 'having given purposefully and with malice aforethought a lethal injection to a terminal patient'.[36] This led to a legal test case that lasted for two years.[37] With this test case the public prosecutor wanted to create clarity with respect to the grey area between hastening death and 'normal' medical treatment.[38] The case caused great concern in the medical profession, as palliative sedation was estimated at that time to be involved in more than 11 000 deaths each year in the Netherlands.[4,39,40] Eventually, in 2006, the court acknowledged that the doctor's treatment was considered normal medical treatment within professional standards.[39,41] Meanwhile, another study brought the Dutch sedation practice to the attention of an international audience and the Dutch government.[42,43] In this study, physicians reported the characteristics of their most recent sedation case. Hastening death was partly the intention of the physician in 47% of cases and the explicit intention in 17% of cases. In its response to this study, the government urged the medical profession to draft a national guideline on terminal sedation, which was launched in 2005 and updated in 2009.[10,44,45] The Royal Dutch Medical Association (RDMA) guideline describes the conditions in which palliative sedation is good medical practice. In addition to defining the professional standard, the guideline also has legal significance. In January 2006, the Public Prosecution Service stated that it saw no reason to prosecute physicians who comply with the RDMA guideline.[46] Although the RDMA guideline gave a comprehensive framework for clinical decision-making, the Dutch debate on the practice of palliative sedation continued. A Dutch study found that continuous deep sedation was administered increasingly more often, whereas the use of euthanasia was decreasing.[47] This study suggested that palliative sedation was possibly being administered as an alternative to euthanasia. In addition to the area of debate concerning the relationship between palliative sedation and euthanasia, other areas of debate were present as well.[40,48-53] First, research has shown that physicians in the past did not always act in accordance with earlier regional guidelines, which served in part as the basis for the RDMA guideline.[54] Several questions therefore arose. Are physicians sufficiently familiar with the RDMA guideline? Is the guideline applied adequately in practice? Another area of debate relates to specific elements of the guideline. When can a symptom be classified as 'refractory'? And do all physicians have the necessary skills to make that judgement? Should it not be compulsory to consult an expert for a second opinion? To what extent is existential suffering an indication for palliative sedation? And regarding the requirement that continuous sedation can only be administered if death is expected within one to two weeks, the question has been raised whether it is possible to estimate time to death.[55-64] Although in 2009 the text of the renewed guideline on these issues was adjusted, and matters such as acute and intermittent sedation, withdrawal of artificial hydration and use of midazolam were clarified, the revision could not answer all questions on the topic. For example, the way in which the patient's comfort should be assessed remained unanswered. Meanwhile, the estimated frequency of CPS has risen from 5.6% of all deaths in 2001 to 12.3% in 2010.[47,65]

The practice of palliative sedation by elderly care physicians

The available studies on palliative sedation involving elderly care physicians indicate that the most common refractory symptoms are pain, dyspnea, delirium, and anxiety.[19,40,43,47,51,54,65-73] The drugs most often administered are benzodiazepines, and in most cases the duration of continuous deep sedation is 7 days or less. In general no life-shortening effect is reported, and artificial hydration is mostly withheld. However, most of these patient-based studies on palliative sedation involving elderly care physicians were published before the introduction and the revision of the RDMA guideline, and data were obtained mostly from limited samples. Furthermore, these studies often neglected to consider the characteristics of nursing home patients separately, who often are elderly patients without cancer.[74]

Unanswered topics: determinants, practice and outcome

In palliative care, the early identification, assessment and treatment of physical, psychosocial and spiritual problems is important in maintaining quality of life.[7] However, little is known about the early identification of patients at high risk for CPS. Hence, to improve the practice of palliative care and CPS in particular, determinants need to be identified that can predict the need for CPS at the end of life. The identification of these determinants could improve advance care planning and quality of life for high-risk patients in a terminal phase; this planning will enhance the patient's autonomy by informing the patient or the patient's representative early in the palliative trajectory about the indication and preconditions for CPS.[75,76] Additionally, the identification of these determinants helps physicians to become aware of high-risk patients early in the palliative trajectory and therefore could enable physicians to respond more rapidly to these patient's symptoms. Effective interventions in these patients could possibly prevent a refractory state for such symptoms, thereby possibly limiting the future need for CPS.

Secondly, elderly care physicians are often involved in end-of-life decision making, including CPS. For 2005, it was estimated that elderly care physicians administered continuous deep sedation in more than 2 000 patients.[6,40] Nevertheless, the number of studies on the practice of palliative sedation administered by this medical specialty is limited, and these studies have several methodological limitations. More insight into the practice of CPS in this medical specialty is essential to contribute to the further development of guidelines and clinical practice. Furthermore, although there is no general consensus on whether palliative sedation is an appropriate intervention for existential suffering, some guidelines and recommendations identify existential suffering as a potential refractory symptom that can be treated with CPS under specific conditions.[10-13,77-79] However, most patient-based studies on existential suffering focus on the frequency of this indication for CPS.[21,54,66,68,69,80-90] Therefore, little insight has been achieved into the practice of CPS for existential suffering and the degree to which the preconditions have been fulfilled.

Finally, there is a need for clinical research on the efficacy of CPS in terms of a person's well-being and control of symptoms.[26,27,29,91,92] The purpose of palliative sedation, whether continuous or intermittent, is to provide comfort to patients with unbearable suffering.[10-13] The gold standard for detecting distress is patient self-reporting.[93] However, patients who are sedated cannot be consulted as palliative sedation produces an impaired capacity to communicate, which places them at a higher risk of unrelieved discomfort. Therefore, the monitoring of palliative sedation through professional assessments is essential to ensure that the patient becomes comfortable while sedated, that the patient receives proportional sedation (not deeper than needed) and to improve communication between professionals and the patients' families.[10,12,13,29,79,94] Although it seems intuitive to monitor the

level of sedation in a sedated patient, the level of suffering should be the primary parameter to be measured.[91] Nonetheless, the "how" of monitoring the level of suffering during palliative sedation is currently an open question. A recent review on published guidelines on palliative sedation shows that only five out of nine guidelines recommend specific assessment methods to monitor palliative sedation, and these are mostly focused on the level of consciousness rather than on discomfort.[91] Furthermore, according to a systematic review, only a minority of patient-based studies on palliative sedation reported the use of observational scales, and most of these scales were used to monitor only the depth of sedation and not the quality.[29] The few scales used in these studies to monitor on the symptom level were based on evaluations by the attending nurse or physician using a Likert or visual analogue scale. Therefore, little is known about the course of discomfort in sedated patients and the efficacy of CPS. Moreover, little is known about determinants of inadequate symptom relief during CPS. Such determinants could help physicians identify patients who are at risk of higher levels of discomfort. In these patients, intensive monitoring and evaluation of the administration of CPS could help to achieve more comfort during the administration of CPS.

Research questions

The objectives of this thesis cover the following topics: the determinants, practice and outcome of CPS. The objectives are specified in the following research questions:

Determinants:

- Which determinants of the administration of continuous palliative sedation are known in the published literature?
- Are age, gender, diagnosis, use of opioids or psycholeptics, number of medications, functional status, symptom distress and level of consciousness at the time of admission to a hospice or nursing home-based palliative care unit associated with the administration of continuous palliative sedation at the end of life?

Practice:

- What is the practice of continuous palliative sedation by Dutch elderly care physicians?
- Do Dutch elderly care physicians fulfil the preconditions for administering continuous palliative sedation in cases in which existential suffering is present?

Outcome:

- What is the course of discomfort in patients admitted to a hospice or nursing home-based palliative care unit receiving continuous palliative sedation?
- Which characteristics of patients admitted to a hospice or nursing home-based palliative care unit determine (dis)comfort during the administration of continuous palliative sedation?

To answer the research questions, we performed a systematic review and designed both a questionnaire and a prospective observational study.

Outline of the thesis

Chapter 2 shows the results of the systematic review of the literature. This chapter describes what was known about the determinants of the administration of CPS and identifies what knowledge was lacking.

Chapter 3 presents the results of the prospective part of our study to investigate which patient-related factors at admission to a hospice or nursing home-based palliative care unit are associated with receiving CPS later in the terminal phase of life.

Chapter 4 shows the results of a questionnaire of elderly care physicians on the practice of CPS.

Chapter 5 focuses on the administration of CPS in cases of existential suffering based on the data obtained from the questionnaire.

Chapter 6 explores the course of discomfort in patients admitted to a hospice or nursing home-based palliative care unit receiving CPS using an observer-based scale. In addition, this chapter analyses which patient characteristics determine (dis)comfort in the final hours of life.

Chapter 7 is a general discussion of the clinical implications of this thesis and future directions for research.

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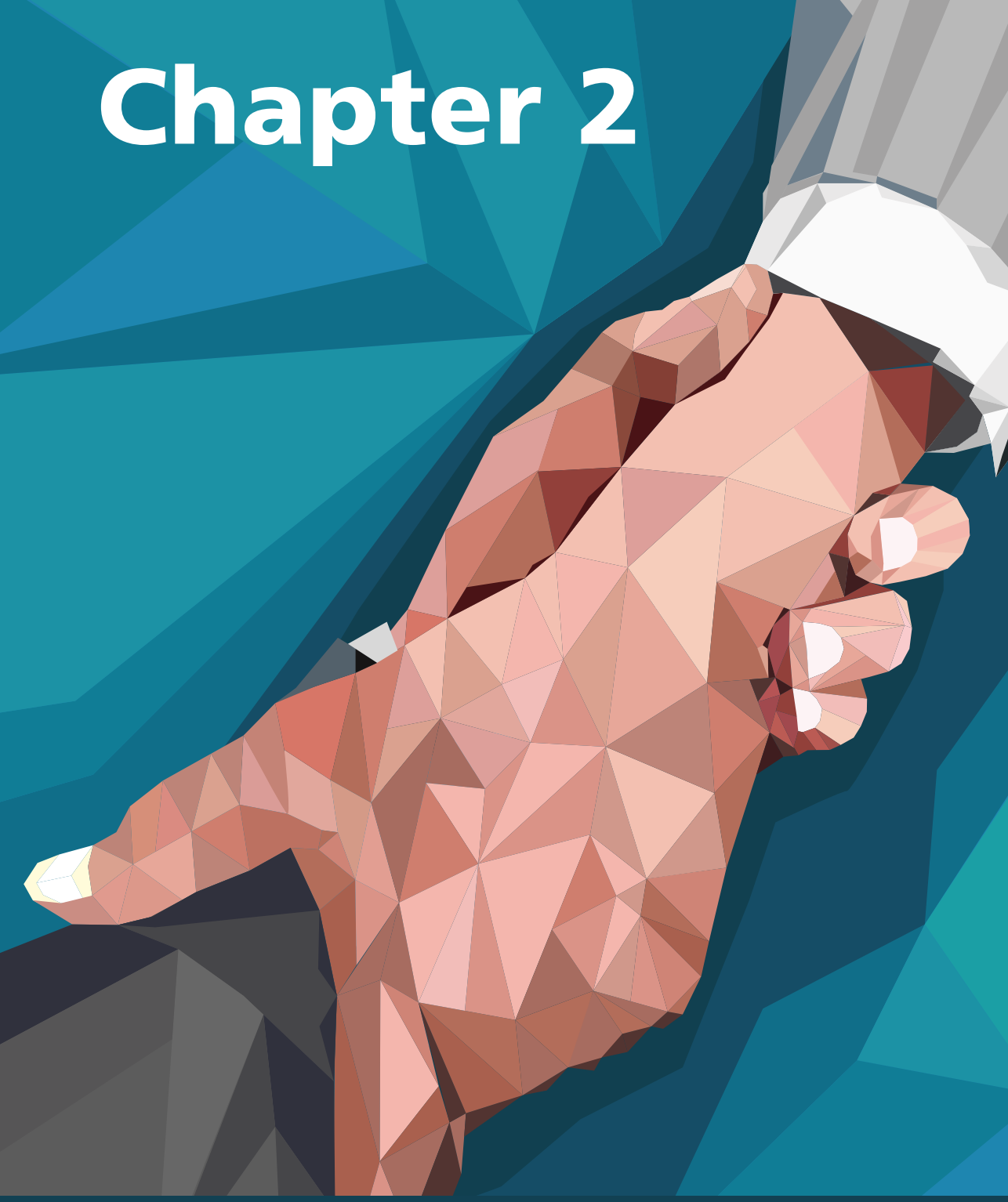
Chapter 2



Determinants of the administration of continuous palliative sedation: a systematic review.

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Chapter 2

Abstract

Background:
Little is known about the determining factors related to the administration of continuous palliative sedation. Knowledge of these determinants may assist physicians in identifying patients who are at high risk of developing refractory symptoms, enable physicians to inform patients, and optimize close monitoring.

Objective:
The aim of this systematic review was to identify determinants of the administration of continuous palliative sedation.

Design:
A systematic review of PubMed, EMBASE, and CINAHL was performed to identify English, Dutch, and German language papers published from January 1990 through April 2011. Inclusion was based on the following criteria: patient-based research on continuous palliative sedation, studies investigating determinants of palliative sedation and/or comparison between sedated and nonsedated cohorts, and studies using multivariate analyses and of fair to good or good methodological quality.

Results:
In total, eight papers were reviewed. The following nine factors were found to be associated with the administration of continuous palliative sedation: younger age, male sex, having cancer, feelings of hopelessness, dying in a hospital, living in a Dutch speaking community setting, very nonreligious or extremely nonreligious physicians, physicians working in "other hospital" specialties, and physicians in favor of assisted death.

Conclusions:
Given the variation in study designs and the limitations of the included studies, the outcomes should be interpreted carefully. Further research is needed, particularly regarding factors that can be influenced and that may alter the course of a patient's symptoms and the patient's eventual need for palliative sedation.

Chapter 2

Introduction

Physicians caring for patients with an advanced disease are often confronted with important end-of-life decisions during the terminal stages of the disease course. The importance of developing advance care plans in the palliative phase has been emphasized; however, many patients and their caregivers still do not discuss possible end-of-life scenarios in the final phases of life.[1] This lack of planning may result in unforeseen situations and difficulties in communication at the bedside when problems arise. In particular, a lack of anticipation that continuous palliative sedation may be administered can lead to undesirable circumstances. Indeed, when patients and their relatives are suddenly confronted with discussions regarding continuous palliative sedation, death, loss of consciousness, and saying goodbye, high levels of stress can be experienced.[2]

Over the past decade there has been considerable discussion concerning the terminology for and definition of palliative sedation. Current definitions include the following similarities:

(1) pharmacological agents used to reduce consciousness,

(2) reserved for the treatment of intolerable and refractory symptoms, and

(3) only considered in a patient who has been diagnosed with an advanced progressive illness.[3–8] The term "palliative sedation" refers to distinct types of interventions: brief or intermittent sedation or continuous sedation administered until death.[3] Continuous palliative sedation may be superficial or deep. In the latter, there is a complete loss of the ability to communicate. The degree of symptom control rather than the degree to which consciousness must be reduced determines the dose, combination, and duration of the drugs administered.[3] Over the past 10 years, continuous palliative sedation has been the subject of considerable debate in the field of palliative care. Questions have arisen as to whether palliative sedation is a euphemism for euthanasia and about where to draw the boundary between sedation for refractory symptoms that are primarily physical and sedation that includes existential suffering.[9–13] Currently, continuous palliative sedation, if correctly applied, is increasingly accepted as a part of medical practice.[4] The frequency of palliative sedation has been reported to range from 2.5% to 64% among terminally ill patients.[14,15] This wide range likely reflects variations in the definition of the term and differences in culture and clinical settings.

Although continuous palliative sedation is not an uncommon end-of-life intervention, little is known regarding the possible determinants of this intervention. A determinant is an element that identifies or determines the nature of something or that fixes or conditions an outcome.[16] Knowing the determinants of continuous palliative sedation could help physicians to better identify patients who are at high risk of developing refractory symptoms and thus optimize the use of close monitoring. Such strategies would allow physicians to respond to a patient's symptoms earlier and to potentially prevent a refractory state of such symptoms, thereby possibly limiting the future need for continuous palliative sedation. Moreover, in acute situations there is often insufficient time to make well-informed, balanced decisions concerning palliative interventions. Thus, the physician must proactively develop a comprehensive care plan and establish end-of-life interventions that will meet the patient's goals, values, needs, and preferences. This planning will enhance the patient's autonomy and inform the patient or the patient's representative about the indication and preconditions for continuous palliative sedation.[17,18] The objective of this study was to perform a systematic review of published literature to identify possible determinants of the administration of continuous palliative sedation.

Chapter 2

Methods

Data sources and search strategy

For this review we searched all articles written in English, Dutch, and German and published from January 1990 through April 2011. A computerized search was performed in PubMed, EMBASE, and CINAHL. The following search terms and combinations were used: (determinant* OR predict* OR correlat* OR characteristic* OR compar* OR associat* OR probability OR survival OR (life AND expectancy)) AND ((palliative AND sedation) OR (terminal AND sedation) OR (sedation AND for AND terminally AND ill AND patients) OR (end AND of AND life AND sedation) OR (continuous AND palliative AND sedation)).

Study selection

To create an initial list of potential studies, the first reviewer (RvD) excluded all studies that reported on the following:

(1) patients who were admitted to an intensive care unit;
(2) palliative sedation that was restricted to children;
(3) sedation therapy for invasive procedures and operations;
(4) sedation therapy in animals; and
(5) medication administered at low doses to relieve insomnia and/or dyspnea or sedation as an unintended side effect of medication.

Subsequently, two reviewers (RvD and JH) independently screened all abstracts that were retrieved, and these two reviewers then applied the following two inclusion criteria:

1. The paper had to report on patient-based research on continuous palliative sedation.
2. The paper had to report on determinants (or terms such as ''associations'' and ''predictors'') of palliative sedation or on a cohort study on sedated and nonsedated patients in a palliative trajectory.

The two reviewers then compared their lists of selected abstracts to reach a consensus. In cases in which there was doubt concerning the inclusion of an article, the full-text article was retrieved. A final list of selected papers was compiled after retrieving the full-text articles that met the inclusion criteria. These papers were then screened for the presence of multivariate statistical analyses, and the methodological quality of the selected papers was assessed using an assessment tool devised by Hawker and colleagues.[19] Only papers that included multivariate analyses and were of fair to good or good methodological quality were included *(see Figure 1)*.

Data extraction

From each selected paper, the following information was extracted: first author, year of publication, research design (prospective or retrospective), setting, patient diagnosis, specialty of the physician, study population, number of included patients who received palliative sedation, depth of sedation, determinants, and outcomes.

Statistical analysis

Because the study design, setting, participants, and reported determinants varied markedly between the studies, we chose to describe the studies, their results, and their limitations rather than combining or ranking the study data using a meta-analytic statistical approach.

Results

Study selection

The search initially identified a total of 1088 unique papers. After an initial screening of the abstracts, 694 papers were excluded, and 394 were deemed eligible for screening by the two reviewers. For 13 of these papers, the reviewers reached immediate consensus that the papers met the inclusion criteria *(see Figure 1)*. For an additional 28 papers, the full-text articles were screened, and 9 of these papers met the inclusion criteria after a consensus meeting. Finally, after screening for the presence of multivariate analysis and fair to good or good methodological quality, 8 of 22 articles were included.

Study characteristics

All of the included studies used a retrospective design. Of the studies that reported on a clinical setting, all combined the settings of hospital and home (see Table 1). Other settings included nursing homes, hospices, palliative care units, institutions, care homes, and other settings. Nearly all of the studies included cancer and noncancer patients. In half of the studies, the specialty of the attending physician was reported. The number of patients to whom palliative sedation was administered varied from 31 to 1260 (total, 3525 patients). All studies focused on deep palliative sedation. Based on Hawker's method, all of the studies had fair to good methodological quality.[19]

Determinants

The studies analyzed a total of 14 factors (see Table 2). Five factors were listed in more than one study—four factors were listed in two studies and one factor was listed in three studies—and nine factors were found in only one study. Five factors showed no significant association with the administration of continuous palliative sedation.[20,21] Of the remaining nine factors, eight showed an increased probability of the administration of continuous palliative sedation. These eight factors were patients who were younger; patients who were male; patients with a cancer diagnosis; patients with feelings of hopelessness; patients dying in a hospital; and patients whose attending physicians were very or extremely nonreligious, working in "other hospital" specialties, or in favor of assisted death.[14,20,22–25] The factor "patients living in a Dutch speaking community setting" showed a decreased probability of receiving continuous palliative sedation.[26]

Discussion

In this review, we found nine factors associated with the administration of continuous palliative sedation. Three studies showed an increased probability of receiving continuous palliative sedation among younger patients.[14,22,23] An explanation for the association between younger age and the administration of continuous palliative sedation could be related to the disease trajectory in such patients. Among younger patients, the average disease trajectory tended to be more aggressive, thus resulting in a higher likelihood of administering palliative sedation.[27] Furthermore, many older patients experience spontaneously diminished consciousness in their final days of life, which may reduce the apparent need for palliative sedation.[28] In addition, because of dementia and inadequate diagnostic tools, signs of pain and other types of suffering may not be well recognized at the end of life among very old patients, which could explain the limited usage of palliative sedation among these patients.[22] For these reasons, we conclude that the association between age and continuous palliative sedation may be the result of an indirect or mediated causal relationship, although the mentioned underlying factors have to be identified as determinants in future research.

Table 1. Studies Concerning Determinants of Continuous Palliative Sedation

Author, year	*Setting*	*Specialty of the physician*	*Study population (number of patients)*	*Patients who received sedation (number)*	*Depth of sedation*	*Determinants*	*Outcome*
Miccinesi et al.,[14] 2006	Hospital, home, institution	NA	20480	1260	Deep sedation[a]	Age, sex, diagnosis, place of death	The probability of receiving sedation was increased in younger patients (<65 years RR 2.34, 95% CI 1.93–2.85; 65–79 years RR 1.91, 95% CI 1.62–2.25), male patients (RR 1.17, 95% CI 1.02–1.34), patients dying from cancer (RR 1.15, 95% CI 1.00–1.33) and in patients dying in a hospital (RR 1.63, 95% CI 1.43–1.86).
Cohen et al.,[25] 2007	Hospital, home, care home (include nursing homes and residential homes for older people), other	NA	8320	605[b]	Deep sedation[a]	Place of death	Continuous deep sedation (with or without administration of (artificial) nutrition and hydration) is more likely to occur in hospital deaths in Belgium ($p < 0.001$) and Sweden ($p < 0.001$).[c]
De Gendt et al.,[22] 2009	Hospital, home, nursing home, other	NA	2127	237	Deep sedation[a]	Age	Terminal sedation (with or without administration of artificial food and fluids) was used less frequently among patients aged 80 years and older (OR 0.424, CI 0.292–0.616).
Van den Block et al.,[26] 2009	Hospital, home (or with family), care home, palliative care unit	General practitioners and hospital specialists	1690	177	Deep sedation[d]	Dutch/French speaking community	Continuous deep sedation (both while administering and forgoing food/fluid) was registered less often in the Dutch speaking than in the French speaking community setting (OR 0.5, 95% CI 0.37–0.69).
Maessen et al.,[24] 2009	Hospital, home, nursing home / hospice	NA	209	31	Deep sedation[e]	Hopelessness	Hopelessness was associated with the decision to pursue continuous palliative sedation ($p = 0.007$).[c]

Van den Block et al.,[21] 2009[f]	Hospital, home, care home, palliative care unit	General practitioners and hospital specialists	1690	177[g]	Deep sedation[h]	Involvement of general practitioner or informal caregiver, treatment goal, content of care	No significant association was found for the involvement of the general practitioner or informal caregiver, the treatment goal or the content of care.
Seale,[23] 2010	Hospital, home, hospice, care home, other	General practitioners, neurologists, specialists in the care of the elderly, specialists in palliative medicine, other hospital specialties	2923	519	Deep sedation[i]	Age, sex, diagnosis, specialty of the physician and attitude of the physician toward assisted death	Significantly higher odds of continuous palliative sedation were reported in patients younger than 60 years (OR 1.62, 95% CI 1.29–2.05), in deaths from cancer (OR 1.4, 95% CI 1.14–1.72), by doctors working in "other hospital" specialties (OR 1.38, 95% CI 1.12–1.71) and doctors being in favor of assisted dying (OR 1.22, 95% CI 1.10–1.36). Sex was not significant.
Seale,[20] 2010	NA	General practitioners, neurologists, specialists in the care of the elderly, specialists in palliative medicine, other hospital specialists	2923	519[j]	Deep sedation[i]	Religious faith, ethnicity of the physician and specialty of the physician	Very or extremely nonreligious physicians were more likely to report having given continuous palliative sedation (OR 1.45, 95% CI 1.02–2.06). Ethnicity and specialty of the physician showed no significant relationship with respect to sedation.

All of the studies used a retrospective design.
Maessen and colleagues included only patients with amyotrophic lateral sclerosis.[24] All other studies included cancer and noncancer patients.
[a]In the article, deep sedation was defined as "The patient received drugs, such as barbiturates or benzodiazepines, to keep him/her continuously in deep sedation or coma until death."
[b]The number was calculated on the basis of the data (the incidence of continuous deep sedation (percentage) and the incidence of end-of-life decisions (number)) in the original article.
[c]The result remained statistically significant in a logistic regression; however, the odds ratios or relative risks were not mentioned in this study.
[d]In the article, deep sedation was defined as "A patient being deeply and continuously sedated or in a coma until death, by means of e.g benzodiazepines or barbiturates."
[e]In the article, deep sedation was defined as "The administration of drugs to keep the patient in deep sedation or coma until death."
[f]Only results reporting continuous palliative sedation "with" or "without" nutrition and hydration with the same outcome were included in this review.
[g]The number of patients who received sedation was not reported in this study, so the number was copied from a study by Van den Block et al.[26] that reported on the same cohort.
[h]In the article, deep sedation was defined as "A patient being deeply and continuously sedated or in a coma until death with drugs such as benzodiazepines or barbituates."
[i]In the article, deep sedation was defined as "A patient is continuously and deeply sedated or kept in a coma before death."
[j]The number of patients who received sedation was not reported in this study, so the number was copied from a study by Seale et al.[23] that reported on the same cohort.
CI, confidence interval; NA, not applicable; OR, odds ratio; RR, relative risk.

With respect to sex, Miccinesi and colleagues stated that it is difficult to explain why male patients are more likely to receive palliative sedation.[14] A study by Caraceni and colleagues, published after April 2011, confirmed the result of Miccinesi and colleagues by showing that palliative sedation was more frequently indicated in male patients (odds ratio 3.2; 95% confidence interval 1.5–7.0).[15] In general, women have different trajectories at the end of life than men. Indeed, women tend to live longer and have a different disease epidemiology and are more likely to receive care in a nursing home at the end of life, which may lead to different medical end-of-life decisions.[29] In addition, at the end of life, men can become more isolated and receive less social support and tend to be more reticent and less willing to discuss emotional and psychological issues, thus making male patients more vulnerable than female patients.[29,30] Although this review's findings regarding sex were inconsistent, the aforementioned factors could contribute to a patient's endurance and may exacerbate symptoms in male patients, ultimately resulting in the administration of palliative sedation. Therefore, sex, although associated, seems to be not an independent determinant but rather a contributing factor because of underlying patterns in the health status of and care for male patients.

Table 2. Summary of Determinants of Continuous Palliative Sedation

Determinants of continuous palliative sedation	*Total number of studies (No.)*	*Consistency of outcomes (direction of factor)*
Patient factors		
Demographic variables		
Age	3	All studies show an increased probability of receiving continuous palliative sedation in younger patients[14,22,23]
Sex	2	One study shows an increased probability of receiving continuous palliative sedation in male patients[14], one study shows no difference in sex[23]
Dutch or French-speaking	1	One study shows a decreased probability of receiving continuous palliative sedation in the Dutch-speaking community setting[26]
Factors related to illness		
Type of disease		
Cancer	2	All studies show an increased probability of receiving continuous palliative sedation in cancer patients[14,23]
Symptoms		
Hopelessness	1	One study shows an increased probability of receiving continuous palliative sedation in patients feeling hopeless[24]
Environmental factors		
Place of death		
Hospital	2	All studies show an increased probability of receiving continuous palliative sedation in patients dying in a hospital[14,25]
Physician		
Religious faith	1	One study shows an increased probability of receiving continuous palliative sedation in patients treated by very or extremely non-religious physicians [20]
Specialty of the physician	2	One study shows an increased probability of receiving continuous palliative sedation in patients treated by doctors working in "other hospital" specialties[23]; one study shows no difference in specialty of the physician[20]
Attitude toward assisted death	1	One study shows an increased probability of receiving continuous palliative sedation in patients treated by doctor in favor of assisted death[23]
Ethnicity of the physician	1	One study shows no significant association regarding the ethnicity of the attending physician and the administration of continuous palliative sedation[20]
Care		
Content of care	1	One study shows no significant association regarding the content of care and the administration of continuous palliative sedation[21]
Involvement		
General practitioner	1	One study shows no significant association regarding the involvement of a general practitioner and the administration of continuous palliative sedation[21]
Informal caregiver	1	One study shows no significant association regarding the involvement of an informal caregiver and the administration of continuous palliative sedation[21]
Treatment		
Treatment goal	1	One study shows no significant association regarding the treatment goal and the administration of continuous palliative sedation[21]

Van den Block and colleagues used language to differentiate between two communities in Belgium and found that although language and culture are strongly related, specific underlying cultural factors, e.g., the degree to which curative, technological, and specialist medicine is appreciated, could more fully explain the difference between patients living in Dutch speaking and French speaking community settings.[26]

Miccinesi and colleagues suggest that palliative sedation is more commonly performed among cancer patients because the clinical condition is more severe in these patients.[14] In addition, cancer patients may experience a more aggressive disease trajectory, and there could be a higher prevalence of refractory symptoms among these patients, thus explaining the association of cancer with a higher probability of receiving continuous palliative sedation.[27,31] Moreover, the end or terminal stage of the disease is better defined in this patient group than in patients suffering from COPD or heart failure.[32] In this case, the cancer diagnosis itself seems to be the explanatory factor that results in an increased likelihood of requiring continuous palliative sedation and therefore can be considered a determinant.

Cohen and colleagues indicated that hospital policies that consider continuous palliative sedation to be an acceptable alternative to euthanasia may be a possible reason for the increased use of palliative sedation in these settings.[25] In addition, Cowan and colleagues found that in the state of Tennessee in the United States, nursing homes, in contrast to hospitals, are often inadequate with respect to the standards of care, protocols, and training that are needed to support palliative sedation. This inadequacy may decrease the prevalence of palliative sedation at these care centers, even in cases in which sedation may actually be indicated.[31] Additionally, when a patient reaches an adequate level of symptom control, the patient is discharged from the hospital to receive end-of-life care in a hospice or at home. Therefore, it is not surprising that patients who are not discharged from the hospital because of complex clinical conditions are presumably more likely to receive palliative sedation prior to dying.[14] It is likely that factors other than being an inpatient determine the administration of palliative sedation, e.g., the patient's symptoms and symptom severity and attitudes toward euthanasia.[23]

Seale and colleagues reported an increased probability of receiving continuous palliative sedation in patients treated by very or extremely nonreligious physicians.[20] It would seem advisable that doctors become more aware of how broader sets of values, such as those associated with religiosity or a nonreligious outlook, may enter into their decision making in end-of-life care.[20]

Maessen and colleagues reported an association between patients' feelings of hopelessness and continuous palliative sedation.[24] However, Maessen and colleagues provided no interpretation of this finding, and no odds ratio was reported.[24] In addition, because patients' proxies retrospectively answered questions about feelings of hopelessness, an under- or overestimation bias may have been present; thus, caution should be used in interpreting this finding.

Seale and colleagues provided no interpretation of their finding that palliative sedation was more likely to be reported by physicians working in "other hospital" specialties.[23] Because the term "other hospital specialties" was not clearly defined, the implications of the outcome of this study are difficult to understand. Additionally, in this study, physicians from several "other hospital" specialties indicated that sedation was provided for reasons other than refractory symptoms.[23] Another study by Seale and colleagues reported on the same cohort as in the aforementioned study and found no difference regarding the use of continuous palliative sedation among physicians from different specialties.[20]

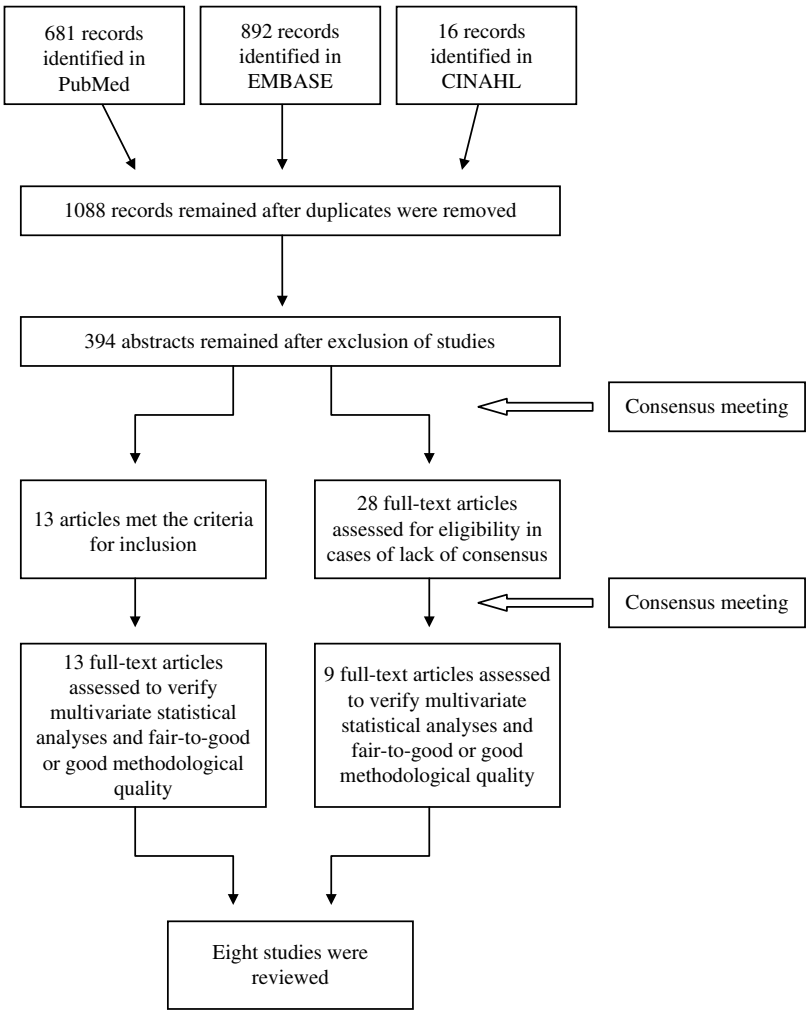

FIG.1. Flow diagram of the studies that were assessed and included.

Strengths and limitations of this study

To the best of our knowledge, this is the first systematic review of published factors associated with the administration of continuous palliative sedation. However, several issues limit the interpretation of the findings in this review. First, several of the studies did not use determinants of palliative sedation as a primary outcome; rather, the studies considered such factors during a secondary analysis of the data. Accordingly, our methodological assessment according to Hawker's method evaluated the aims, methods, analysis, results, and implications of research questions that were not directed toward the purpose of our review. Second, all of the reviewed studies were retrospective and primarily used questionnaires with response rates varying between 42% and 75%, which carry their own associated limitations because of recall bias and nonresponder bias. Moreover, in this type of study, it is only possible to examine associations; cause-and-effect relationships cannot be studied.

Third, several of the findings were based on the answers of patients' proxies or based on information from general practitioners who provided information about patients who died in the hospital, thus making the findings susceptible to under- or overestimation bias. Fourth, all included studies focused on continuous deep palliative sedation, whereas the objective of this study was to identify the determinants of the administration of continuous palliative sedation in general, which potentially limits extrapolation from the studies. Additionally, the study designs varied with respect to population, setting, and attending physician, all of which make comparisons difficult and limit the generalizability of the results. Fifth, in several studies, multivariate calculations of an odds ratio or relative risk were lacking, and descriptions of the statistical methods were inadequate, e.g., information on the factors used in the multivariate models was absent. In addition, none of the multivariate models included factors such as the patient's symptom severity. Moreover, comparing one determinant across several studies can be problematic because of differences in the underlying multivariate models and the number and types of factors used in the analyses. Furthermore, the results of different studies regarding the same determinant are not always consistent. Finally, there is wide variation in terminology for independent variables. Terms such as "determinant" or "predictor" are often used in the literature, even in cases in which a causal relationship is not present. In such cases, terms such as "association" or "correlation" would be more appropriate.

Conclusions

Although the literature suggests that there are several determinants of the administration of continuous palliative sedation, this review uncovered important gaps in our current understanding of these determinants and even questioned whether the identified factors are actually determinants or would be better labeled as factors associated with the administration of continuous palliative sedation. This gap in our current understanding of the mechanisms leading to continuous palliative sedation limits our ability to offer proactive care to patients requiring palliative measures. In particular, determinants that can be acted upon early in the clinical palliative care trajectory are more relevant from a clinical perspective, e.g., factors such as medication, symptoms, and symptom severity. In such cases, appropriately applied interventions can alter the course of symptoms and the patient's eventual need for palliative sedation. However, knowledge of determinants of the administration of continuous palliative sedation does not exclude the need for qualified personnel. Physicians must be competent in the assessment of symptoms and the symptoms' correct treatment prior to starting continuous palliative sedation and in the administration and evaluation of continuous palliative sedation.

Future research regarding determinants of the use of palliative sedation should be performed using a prospective multicenter study design and a research protocol that includes clear and timely baseline measurements during the patient's trajectory, e.g., at admission to a hospital. Such studies should use a multivariate analysis after clearly defining continuous palliative sedation and should focus on clinically relevant determinants.

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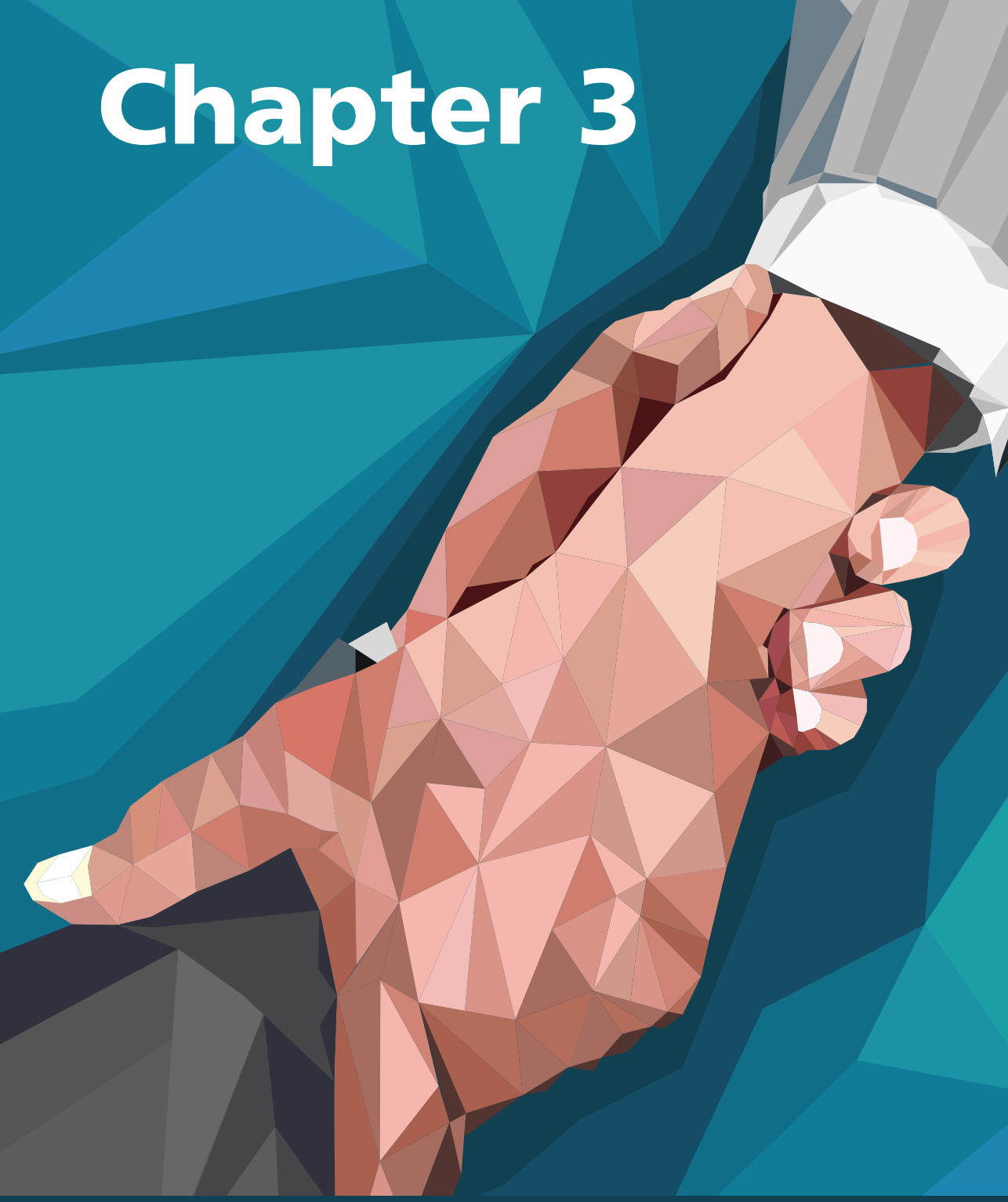
Chapter 3



Patient-related determinants of the administration of continuous palliative sedation in hospices and palliative care units: a prospective, multicenter, observational study.

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Chapter 3

Abstract

Context.
Knowledge of determinants that are associated with the administration of continuous palliative sedation (CPS) helps physicians identify patients who are at risk of developing refractory symptoms, thereby enabling proactive care planning.

Objectives.
This study aims to explore which patient-related factors at admission are associated with receiving CPS later in the terminal phase of life.

Methods.
A prospective multicenter observational study was performed in six Dutch hospices and three nursing home-based palliative care units. The association between patient-related variables at admission (age, gender, diagnosis, use of opioids or psycholeptics, number of medications, Karnofsky Performance Status scale score, Edmonton Symptom Assessment System distress score, and Glasgow Coma Scale score) and the administration of CPS at the end of life was analyzed.

Results.
A total of 467 patients died during the study period, of whom 130 received CPS. In univariate analysis, statistically significant differences were noted between the sedated and nonsedated patients with respect to younger age ($P = 0.009$), malignancy as a diagnosis ($P = 0.05$), higher Karnofsky Performance Status score ($P = 0.03$), the use of opioids ($P < 0.001$), the use of psycholeptics ($P = 0.003$), and higher Edmonton Symptom Assessment System distress score ($P = 0.05$). Multivariate logistic regression analysis showed that only the use of opioids at admission (odds ratio 1.90; 95% confidence interval 1.18-3.05) was significantly associated with the administration of CPS.

Conclusion.
Physicians should be aware that patients who use opioids at admission have an increased risk for the administration of CPS at the end of life. In this group of patients, a comprehensive personalized care plan starting at admission is mandatory to try to prevent the development of refractory symptoms. Further research is recommended, to identify other determinants of the administration of CPS and to investigate which early interventions will be effective to prevent the need for CPS in patients at high risk.

Chapter 3

INTRODUCTION

Patients with a terminal illness can experience severe symptoms during the last phase of their lives. For some patients, these symptoms become unbearable and refractory, and palliative sedation becomes a last-resort treatment option.[1,2] Although there is still a lack of consensus on a definition, palliative sedation has been defined as "the deliberate lowering of a patient's level of consciousness in the last stages of life" and refers to brief, intermittent, or continuous sedation.[3] Continuous palliative sedation (CPS) aims to reduce proportionally the consciousness of the patient until the moment of death.[3] Although CPS can be administered as a medical intervention at the end of the continuum of palliative care, it must be seen as a last-resort intervention.[4,5] CPS not only takes away a patient's suffering, deep CPS also takes away any potential positive and meaningful experiences a patient might have.[1,6-9] Besides, research shows that relatives, nurses, and physicians sometimes experience the administration of CPS as a burden.[10,11]

In palliative care, the early identification, assessment, and treatment of physical, psychosocial, and spiritual problems are important in maintaining quality of life.[12] However, little is known about the early identification of patients at high risk for CPS.[13] Hence, to improve the practice of palliative care and CPS in particular, it is useful to identify patient-related determinants early in the palliative trajectory, associated with the administration of CPS at the end of life. The identification of these determinants could improve advanced care planning and quality of life for high-risk complex patients in a terminal phase. It may help physicians to inform these patients early in the palliative trajectory about the possibility of the administration of CPS in case refractory symptoms occur in the last two weeks of life. In addition, the identification of these determinants helps physicians to become timely aware of and respond to an increased risk of the development of a complexity of symptoms in palliative patients leading to refractory suffering. Early effective interventions in these patients could possibly prevent or decrease the need for CPS.

Therefore, the objective of this study was to identify patient-related determinants of the administration of CPS at admission to a hospice or nursing home-based palliative care unit (PCU). Based on our previously reported review and clinical relevance, we hypothesize that age, gender, diagnosis, use of opioids or psycholeptics, number of medications, functional status, symptom distress, and level of consciousness on admission could be associated with the administration of CPS.[13]

Methods

Setting and Patient Population

This study involved a prospective observational multicenter study in six hospices and three nursing home PCUs in The Netherlands. Patient admission to these settings is based on an estimated life expectancy of less than three months, according to the referring physician. Inclusion criteria for the study were any new admission during study episode, written informed consent, and an age of 18 years or older.

Data Collection and Follow-Up

Data were collected between the first of March 2011 and the first of March 2013 and included a follow-up period of three months. Data collection ended when the patient died, was discharged, or at the end of the study period.

Measures/Assessments

The patient's functional status was evaluated using the Karnofsky Performance Status (KPS) scale.[14] The Dutch-translated version of the KPS is a descriptive ordinal scale that rates the patient's functional status in 10-point intervals ranging from normal functioning (100) to dead (0).[15] The validity and reliability of the KPS have been shown in patients admitted to a hospice and in cancer patients.[16,17]
The level of consciousness of the patient was evaluated using the Glasgow Coma Scale (GCS).[18] The GCS has three subscales: eyes, movement, and verbal reactions. The score ranges from 15 (normal consciousness) to 3 (deep comatose). The GCS has good psychometric properties, and its wide use supports the application of the GCS in this study.[19-23]
To assess symptom severity, the Edmonton Symptom Assessment System (ESAS) was used.[24] This scale consists of nine 100-mm visual analogue scales assessing pain, activity, nausea, depression, anxiety, drowsiness, appetite, sensation of well-being, and shortness of breath.[24] Higher scores reflect greater symptom severity. The symptom distress score is calculated by summing the nine individual symptom scores. The assessment is completed by the patient. In case of a decision-incompetent patient, a family member or nurse completed the ESAS. In this study, a validated Dutch version was used.[25] Although more psychometric research has been advised, the ESAS has been widely adopted in palliative care programs for clinical and research purposes and is a well-recognized and commonly used standard assessment tool for pain and symptom assessment.[26]
The study protocol required completion of the assessments within five days after admission, to prevent contamination of the patient-related factors with clinical interventions from the attending physicians and nurses. Nurses registered the date of admission, gender and age of the patient, KPS, medication use, and GCS on admission. In addition, nurses instructed patients for completing the ESAS. The attending physician recorded the patient's diagnosis using the International Statistical Classification of Diseases and Related Health Problems 10th Edition.[27] Diagnosis was defined as "disease(s) which influenced the health status of the patient at admission." Furthermore, in case the patient died, the physician registered the date of death and whether CPS was administered. Palliative sedation was defined according to the Dutch national guideline, and CPS was defined as "palliative sedation administered until death."[3] This definition excluded situations in which medication was administered in normal doses to relieve insomnia and/or anxiety, where sedation was an unintended side effect of medication or where palliative sedation was only administered temporarily.

The attending physician determined the indication for CPS and the doses, combinations, and duration of the drugs administered. Furthermore, the research protocol did not formalize the discussion with the patient or their representative concerning advanced care planning and CPS. The physician was free in the way he discussed these items, but to get acceptance of the study, obviously, CPS and the possible reasons to start this intervention were discussed at admission.

Training

The first author (R. H. P. D. v. D.) provided a halfday training session for the participating nurses and physicians separately. The nurses practiced the assessments using vignettes. Instruction was given on the case report forms and the period of time to complete the assessments. The definitions in the study protocol were explained to the physicians, and patient cases were used to clarify the criteria for CPS.

Ethical Considerations

The study followed guidelines for good clinical practice and was conducted after approval of the research ethics committee of the Radboud University Medical Centre (ref 2010/407). Patients or their representatives (in cases of a decision-incompetent patient) were invited to participate via oral and written information. For patients who did not participate, only anonymous demographic data were collected for the purpose of nonresponder analysis.

Statistical Analysis

The primary outcome was the administration of CPS. Patients who died were categorized into two groups; those who did and those who did not receive CPS. Patients who were discharged or who were still alive after the follow-up period were excluded from further analyses. When one or two symptoms were missing from the ESAS, the symptom distress score was calculated via the imputation of the mean score of the known symptoms per patient, so-called ipsative mean imputation.[28] When the ESAS was completed later than five days after admission or when there were more than two missing symptoms, the ESAS symptom distress score was considered missing.

Medication was categorized as opioids (Anatomical Therapeutic Chemical classification N02A); psycholeptics (Anatomical Therapeutic Chemical classification N05); and the total number of drugs with the exclusion of ophthalmic, cutaneous, and rescue medications.

We compared patients who were sedated and who were not on characteristics at admission using independent sampled t-tests and Pearson's chi-square tests. To assess the independent relationship of the characteristics at admission and the administration of CPS (yes/no), we used a multiple logistic regression model. To take into account the clustering of patients in hospices and PCUs, the location was included in the model.

To handle missing data, we used multiple imputation creating five imputed data sets. All patient characteristics including location were included in the imputation procedure. We combined the results of the multiple logistic regression models across the five data sets. As a sensitivity analysis, the outcome of the multivariate model without using multiple imputation was also assessed.

The probability of being sedated was calculated in odds ratios (ORs) with 95% CIs. P-values were two-sided, and an alpha <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 20.0.0 (SPSS, Inc., Chicago, IL).

Results

Patients

During the study period, of 803 patients admitted to the participating hospices or PCUs, 503 patients gave written informed consent. The included patients (n = 503) did not differ from the excluded patients (n = 300) with regard to gender, age, KPS score (P = 0.20, P = 0.12, P = 0.34, respectively, data not shown) or one of the diagnoses. At the end of the study, four included patients remained alive and 32 included patients had been discharged. A total of 467 patients died and were included for further analysis; 130 of these patients (27.8%) received CPS (Fig. 1). This percentage, with a range of 13.5%-48.1%, was associated with location (Pearson's chi-square 33.802, df = 8, P < 0.001). The mean duration from admission until death for the 467 patients was 33.5 days (SD 42.7) with a median duration of 19 days (range 0-305). No significant differences between nonsedated (mean 33.1 days [SD 43.3]) and sedated patients (mean 34.8 days [SD 41.2]) were observed (P = 0.70).

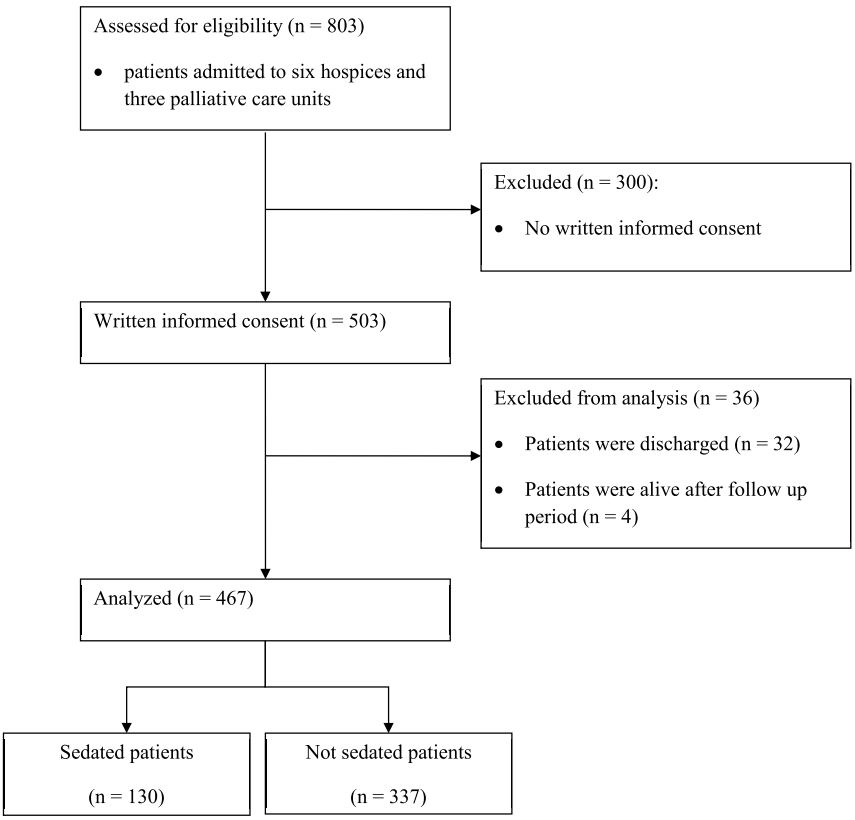

Fig. 1. Flowchart of patients throughout the study.

Population and Univariate Analysis

At admission, more than half of the study population consisted of patients aged 76 years and older, having cancer, with a KPS score of 40 or less, and a GCS score of 13 or more. The distribution of men and women was similar. Half of the patients (50.2%) used one or more opioids, and 42.2% of the patients used psycholeptics. The mean number of drugs used was 5.7 (Table 1).

Statistically significant differences were noted between the sedated and nonsedated patients with respect to younger age, malignancy as a diagnosis, higher KPS score, the use of opioids, or the use of psycholeptics (Table 1).

For the ESAS, for two patients more than two symptoms were missing, the ESAS was not completed by 53 patients and 71 patients completed the ESAS later than five days after admission. In univariate analysis, the mean ESAS distress score at admission was significantly higher in the sedated group than in the nonsedated group (Table 1).

Table 1
Patient-Related Characteristics at Admission to a Hospice or a Palliative Care Unit for Patients Who Were Sedated During Admission and Those Who Were Not

Variable	Population (n = 467)	Sedated (n = 130)	Not Sedated (n = 337)	Pvalue
Age, number (%)				**0.009**[a]
<55 yrs	23 (4.9)	12 (9.2)	11 (3.3)	
55–75 yrs	188 (40.3)	57 (43.8)	131 (38.9)	
>75 yrs	256 (54.8)	61 (46.9)	195 (57.9)	
Gender, number (%)				0.78[a]
Male	224 (48.0)	61 (46.9)	163 (48.4)	
Female	243 (52.0)	69 (53.1)	174 (51.6)	
Malignant neoplasms, number (%)				**0.05**[a]
No malignant neoplasms	76 (16.3)	14 (10.8)	62 (18.4)	
Malignant neoplasms	391 (83.7)	116 (89.2)	275 (81.6)	
Glasgow Coma Scale (GCS), number (%)				0.09[a]
Score 3–6	18 (4.1)	2 (1.6)	16 (5.1)	
Score 7–12	45 (10.2)	9 (7.2)	36 (11.4)	
Score 13–15	378 (85.7)	114 (91.2)	264 (83.5)	
Karnofsky score, number (%)				**0.03**[a]
Score 0–40	368 (79.0)	101 (77.7)	267 (79.5)	
Score 50–70	93 (20.0)	25 (19.2)	68 (20.2)	
Score 80–100	5 (1.1)	4 (3.1)	1 (0.3)	
Opioid use, number (%)				**<0.001**[a]
No opioid use	231 (49.8)	46 (35.4)	185 (55.4)	
Opioid use	233 (50.2)	84 (64.6)	149 (44.6)	
Psycholeptics use, number (%)				**0.003**[a]
No psycholeptics use	268 (57.8)	61 (46.9)	207 (62.0)	
Psycholeptics use	196 (42.2)	69 (53.1)	127 (38.0)	
Number of medications, mean (SD)	5.7 (3.5)	6.1 (3.2)	5.5 (3.6)	0.06[b]
ESAS distress score 9, mean (SD)	37.5 (15.4)	40.1 (16.2)	36.4 (15.0)	**0.05**[b]

ESAS = Edmonton Symptom Assessment System.
Data were missing for the Karnofsky score in one patient, on opioids, psycholeptics, and number of medications for three patients.
For ESAS, 126 patients were excluded in univariate analysis: six symptoms were missing for one patient, eight symptoms for one patient, and all symptoms for 53 patients. Seventy-one patients completed the scale later than five days after admission. Ipsative mean imputation was used in 20 patients: one symptom was missing for 19 patients, two symptoms for one patient. There was no significant difference in the distribution of missing data between the sedated and nonsedated groups.
Data on GCS were missing for 26 patients.
Values in bold are significant.
[a]Chi-square test.
[b]Student t-test.

Multivariate Analysis

Multivariate logistic regression analysis showed that the use of opioids at admission was significant associated with the administration of CPS (OR 1.90; 95% CI 1.18-3.05; P = 0.008; Table 2). Sensitivity analysis, using a model without multiple imputation, also identified the use of opioids at admission (OR 1.98; 95% CI 1.13-3.46; P = 0.017; data not shown).

Table 2
A Multiple Logistic Regression: Determinants of Continuous Palliative Sedation, Measured at Admission to a Hospice or a Palliative Care Unit (n = 467)

Determinant	Direction (Reference)	Odds Ratio	95% CI	*P*-value
Gender	Male (female)	0.97	0.62−1.52	0.91
Malignant neoplasms	Present (not present)	1.42	0.68−2.93	0.35
Opioid use	Present (not present)	1.90	1.18−3.05	**0.008**
Psycholeptics use	Present (not present)	1.57	1.00−2.49[a]	0.05
Age	Older[b]	0.98	0.96−1.00[a]	0.12
Karnofsky score	Higher[b]	1.06	0.86−1.29	0.59
Glasgow Coma Scale	Higher[b]	1.10	0.96−1.27	0.16
Number of medications	Higher[b]	1.02	0.95−1.09	0.60
ESAS	Higher[b]	1.01	0.99−1.03	0.24

ESAS = Edmonton Symptom Assessment System.
Nagelkerke R square 0.19.
Values in bold are significant.
[a]For psycholpetics, the CI to three decimal places was 0.996 to 2.489, with a *P*-value of 0.052. For age, the CI to three decimal places was 0.964 to 1.004, with a *P*-value of 0.115.
[b]Continuous variable.

Discussion

To our knowledge, this is the first study to prospectively investigate the association between patient-related characteristics at admission and the eventual administration of CPS. We found that only the use of opioids at admission in hospices and nursing home PCUs was independently positively associated with the administration of CPS. No statistically significant independent association was found for gender, age, use of psycholeptics, diagnosis of malignancy, KPS score, GCS score, ESAS symptom distress score, or number of medications on admission.

Results in Relation to Other Studies and Potential Mechanisms

The positive independent association between CPS and the use of opioids at admission could indicate that specific symptoms treated with opioids (such as pain or dyspnea) were more difficult to control in these patients in the palliative trajectory.[29] Caraceni et al.[30] reported that palliative sedation was more frequently indicated in patients with recurrent dyspnea in the last seven days of life (OR 4.2; 95% CI 1.9-9.2). Therefore, dyspnea and pain could be the underlying determinants for CPS rather than the use of opioids as such. Additionally, a direct causal relationship between opioid use and

CPS could be present because of opioid-induced delirium, which in turn may result in the need for CPS.[30-32] Interventions such as opioid rotation and regular screening for and treatment of delirium could reduce the eventually need for CPS in such cases. Patients with opioid use at admission should be informed about the possible side effects of this medication, the need of regular evaluation, and the possible interventions when side effects occur, with CPS as a last-resort intervention. In The Netherlands, the vast majority of the general public accepts the use of palliative sedation at the end of life, although the term palliative sedation is not well known among the general public.[33] The finding that many people do not know the term palliative sedation emphasizes the importance to clearly inform patients and relatives about palliative sedation and to verify their beliefs on and expectations of palliative sedation. Information should include that palliative sedation is a last-resort intervention for refractory suffering, that the life expectancy of a patient may not exceed 2 weeks at the moment CPS is started and that CPS has to be distinguished from euthanasia.[3]

Previous retrospective studies did not focus on an association between the use of psycholeptics and the administration of CPS.[13] In this study, the use of psycholeptics at admission showed a marginally significant association with the administration of CPS. Psycholeptics, for example, haloperidol, are usually prescribed for the management of delirium in palliative care.[34] Agitated delirium tends to worsen over time and often becomes refractory in the terminal phase leading to palliative sedation.[35] For this reason, we assume that the association between the use of psycholeptics at admission and CPS could be a surrogate of an underlying delirium.

When approaching the terminal phase of life, symptoms may exacerbate other symptoms or evolve into a cascade of symptoms; this may lead to a situation in which the patient eventually experiences unbearable and refractory suffering, and an indication for CPS arises.[3] Therefore, our hypothesis was that a higher symptom distress score at admission would be a risk factor. However, the results of this study did not support this hypothesis. It is possible that specific symptoms such as pain or agitation, rather than the aggregated score, could have influenced the chance of CPS. The sample size of our population, although considerable for palliative care research, did not allow for a subanalysis of individual symptoms or clusters, that is, the use of opioids and the symptoms pain and dyspnea.

In contrast to previous retrospective studies, the multivariate analysis in our prospective study did not confirm an association between male or younger age patients and the administration of CPS.[30,36-39] However, our study population differed from the retrospective studies by including only a small number of young adults and being restricted to a hospice and nursing home PCU setting.[30,36-39] Literature reports an association between the presence of cancer and the administration of CPS.[37-39] None of these retrospective studies included symptoms or symptom distress scores in their multivariate model.[37-39] In the univariate analysis, our study demonstrated significant differences between the sedated and nonsedated patients regarding the diagnosis of malignancy; however, the multivariate analysis did not confirm this association.

Although we focused on patient-related factors, this study showed also that location is associated with the administration of CPS. The umbrella term location makes it difficult to identify the specific underlying factors of this term. A review on determinants of CPS from the literature showed that the following non-patient-related factors were associated with the administration of CPS: very or extremely nonreligious physicians, physicians working in "other hospital" specialties, physicians in favor of assisted death, and Dutch-speaking community setting in Belgium.[13] Besides, other

characteristics of health care providers and characteristics of location, that is, what is allowed in a location based on the religious affiliation, could also be an explanatory factor that results in differences in the administration of CPS between locations. Furthermore, the "how" of determining intolerability of suffering and refractoriness is not established in guidelines.[40] This can result in subjectivity in determining the refractoriness of symptoms and therefore in variation of the eventually administration of CPS. Our study was not intended to find location-dependent variables, but our results underline the need to perform such a study in the future.

Strengths and Limitations

A strength of this study was its prospective multicenter design, the clear operational definition of CPS and the use of validated, clinically relevant assessments at a well-defined time point. Additionally, the large number of sedated patients made it possible to look at the independent relationship of multiple characteristics at admission and the administration of CPS in the terminal phase of life.[41]

Nevertheless, some limitations of this study warrant attention. First, an important limitation of this study is the number of protocol violations and missing components of some patients' ESAS, which influenced the power of the study and therefore its validity. However, multivariate models with and without multiple imputation were used to control for understating uncertainty. These models showed a similar association between the administration of CPS at the end and the use of opioids at admission.

Second, assessments were performed at admission to identify patients who were at risk of developing refractory symptoms at the end of the palliative trajectory. However, we could not determine whether the associations found in this study were time sensitive or not.

Third, 503 of 803 patients (62.6%) participated in our study. Although the 503 patients were a representative sample regarding gender, age, KPS, and diagnosis of the total population, nonresponder bias cannot be excluded.

Fourth, the reported variability in the administration of CPS in our study could reflect a different understanding of CPS among the participating physicians and nurses. However, we did all efforts to minimize this, by providing a training where the definitions in the study protocol were explained and patients' cases were used to clarify the criteria for CPS. Furthermore, previous reported research on palliative sedation showed that almost all physicians reported that they knew about the Dutch national guideline and mostly rated their level of level of knowledge about the contents of the guideline as good to excellent.[42]

Finally, this study was performed in hospices and nursing home PCUs in The Netherlands. Most patients were aged 76 years and older with a low Karnofsky index, reflecting a relatively low functional status. The findings in this study may not be generalizable to other populations, care settings, and countries.

Conclusion

This study showed that the use of opioids at admission to a hospice or PCU was independently positively associated with the chance of the administration of CPS. In patients with this characteristic, physicians should be aware of the higher risk of developing refractory symptoms leading to CPS in the terminal phase of life, and a comprehensive care plan, including end-of-life interventions that meet the patient's goals, values, needs, and preferences, should be developed early in the palliative trajectory. Besides, physicians should inform these patients early in the palliative trajectory about the possibility of the administration of CPS in case refractory symptoms occur in the last two weeks of life. This study was not performed to unravel the specific underlying symptoms or mechanism that increases the chance of patients with opioid usage to develop refractory symptoms in the end stage of life. Further studies will be necessary to find such mechanisms. Furthermore, such research should find other determinants of the administration of CPS, involving different settings and populations, and finally examine if interventions based on such knowledge will be effective to prevent the development of refractory symptoms in the terminal stage of life of these high-risk patients, and eventually the need for CPS.

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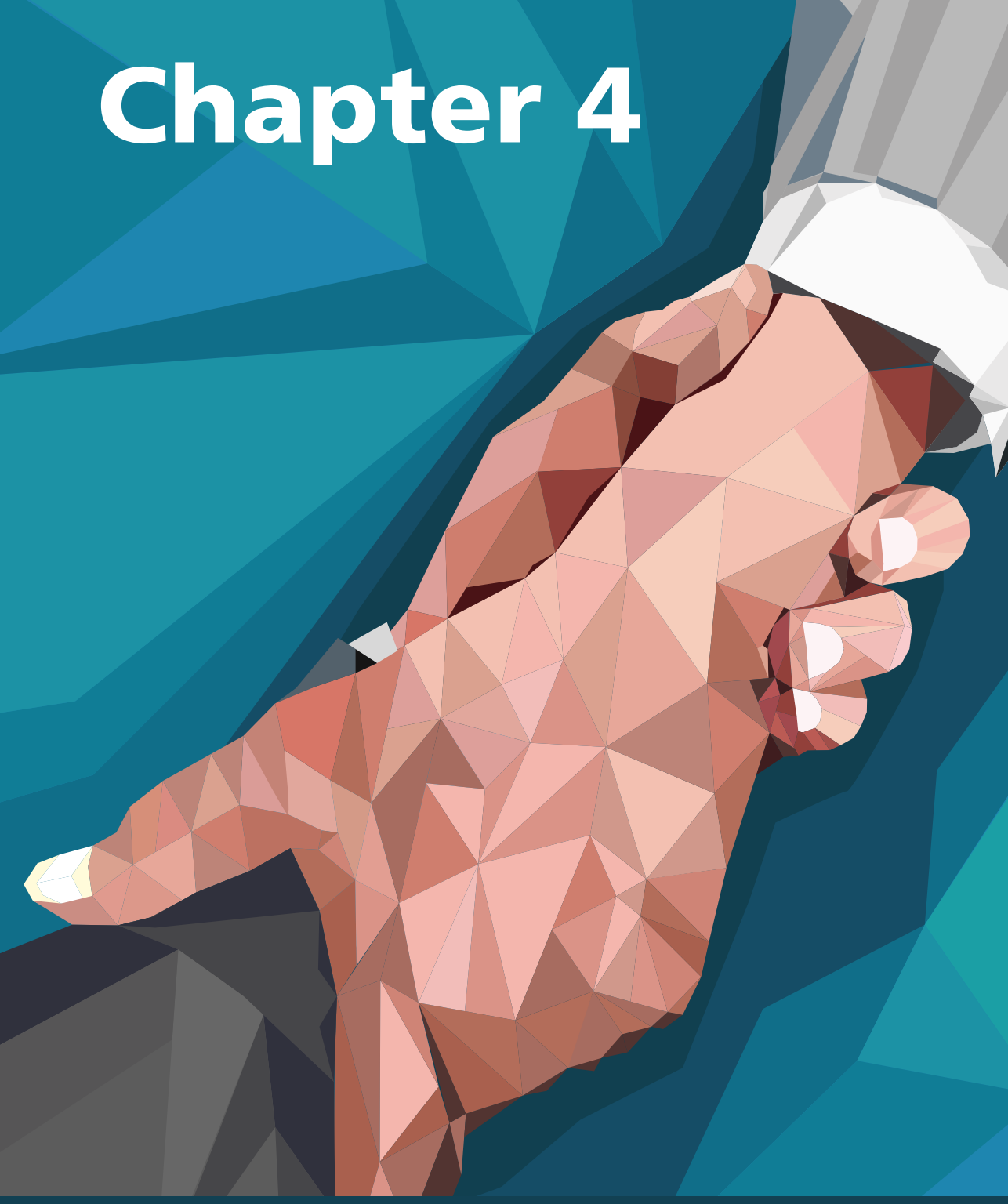
Chapter 4



The practice of continuous palliative sedation in elderly patients: a nationwide explorative study among Dutch nursing home physicians.

van Deijck RH, Krijnsen PJ, Hasselaar JG, Verhagen SC, Vissers KC, Koopmans RT.
J Am Geriatr Soc 2010;58(9):1671-8

Chapter 4

Abstract

Objectives:
To study the practice of continuous palliative sedation (CPS) by Dutch nursing home physicians in 2007.

Design:
A structured retrospective questionnaire.

Setting:
Nationwide nursing home physician study in the Netherlands.

Participants:
One thousand two hundred fifty-four nursing home physicians received a questionnaire concerning their last case of CPS in 2007; 54% (n = 675) responded.

Measurements:
Characteristics of CPS and requests for euthanasia were measured.

Results:
Three hundred sixteen patients were described. The majority had cancer or dementia. The most-reported refractory symptoms were pain (52%), anxiety (44%), exhaustion (44%), dyspnea (40%), delirium (24%), loss of dignity (18%), and existential distress (16%). In 98% of cases, CPS was aimed at symptom relief. Of patients with cancer, 17% had previously requested euthanasia. The mean starting dose of midazolam was 31 mg every 24 hours (range 0–240 mg/24 h), and the mean end dose was 48 mg every 24 hours (range 0–480 mg/24 h).

Conclusion:
In addition to physical symptoms, anxiety, exhaustion, loss of dignity, and existential distress are often mentioned as refractory symptoms in the decision to start CPS by nursing home physicians. Furthermore, close to one in five patients with cancer had made a previous request for euthanasia. The dosage range of midazolam in this study fits the recommendations of the Dutch national guideline on palliative sedation, although international studies show smaller dosage ranges. Finally, prospective research about the acceptability and assessment of nonphysical symptoms as indications for CPS is recommended.

Chapter 4

INTRODUCTION

Since the 1990s, there has been a growing interest in palliative care in the Netherlands. Although historically administered in people with cancer, palliative care is increasingly administered to patients without cancer too. Despite improvements in palliative care, some symptoms remain hard to treat or relieve. If one or more symptoms in a patient who is dying cause unbearable suffering, and conventional modes of treatment are not effective or fast acting enough (so-called refractory symptoms), an indication arises to administer palliative sedation.

The third national Dutch study on end-of-life decisions was the first to report on the practice of what was then referred to as terminal sedation in the Netherlands.[1] In response to this study, the Dutch government stressed the need for a national guideline on palliative sedation.[2] In 2005, the Royal Dutch Medical Association (RDMA) issued a national guideline on palliative sedation.[3,4] Despite this guideline, the practice of palliative sedation remained a controversial subject. Furthermore, a Dutch study found that continuous deep sedation was being used increasingly more often, whereas the use of euthanasia was decreasing.[5] This suggested that palliative sedation was possibly being administered as an alternative to euthanasia.

Although the RDMA guideline gives a comprehensive framework for clinical decision-making, the recommendations are mainly expert-based. The methodological, practical, and ethical challenges involved limit research on palliative sedation. In particular, research on palliative sedation in a population of frail and elderly patients has proved to be problematic for nursing home physicians. The available studies indicate that the refractory symptoms are mostly anxiety, pain, and dyspnea. The drugs most often administered are benzodiazepines, and in most cases the duration of continuous deep sedation is 7 days or less, no life-shortening effect is reported, and artificial hydration is withheld.[5–13] In 2005, it was estimated that nursing home physicians used continuous deep sedation in conjunction with end-of-life decisions in 5.9% of all deaths.[7] However, all but one of these studies originated from before the introduction of the RDMA guideline, and data were obtained mostly from limited samples. Furthermore, these studies often neglected to consider the practices of nursing home physicians (characterized by a large percentage of elderly patients without cancer) separately from other care settings such as hospitals and home care (with mainly patients with cancer).[14] Nursing home physicians find it difficult to define patients as terminally ill or to predict their life expectancy, and the pattern of symptom prevalence is different from that of patients with cancer.[14] It was therefore hypothesized that in patients with cancer, the refractory symptoms for continuous palliative sedation (CPS) would differ from those of patients without cancer. Moreover, the difficulty of predicting life expectancy of people without cancer could complicate the administration of CPS, because a precondition for its use within the RDMA guideline is that death will ensue within 1 to 2 weeks. More insights into this specific group of patients shall contribute to the further development of guidelines on palliative sedation and could provide more targeted palliative care. There is an international demand for more research on monitoring national trends and patterns in end-of-life care, such as (continuous) palliative sedation, including the administration of artificial nutrition and hydration, the drugs and dosages administered, and the interval between the administration of sedating drugs and death.[15,16]

The practice of CPS by Dutch nursing home physicians was therefore investigated in a nationwide study. Special attention was paid to differences in the administration of CPS to the subgroups of patients with cancer and dementia.

METHODS

Respondents

All registered members of the Dutch Association of Nursing Home Physicians were eligible for the study (n = 1,441). Because of a parallel ongoing study on palliative sedation in the Amsterdam and Rotterdam regions, 187 of the 292 members in this region were excluded. A structured retrospective questionnaire was sent to the remaining 1,254 nursing home physicians in February 2008. A return envelope was sent with the questionnaire, and full confidentiality was assured. After 3 weeks, all physicians received a reminder to return the questionnaire so as to maximize the response rate. Data collection ended in May 2008.

Questionnaire

The questionnaire was a revised version of a previously reported questionnaire.[9] The original questionnaire was adapted to nursing home patients and piloted by 20 nursing home physicians, which resulted is some minor modifications. In the questionnaire, palliative sedation and refractory symptoms were defined according to the RDMA national guideline.[3] Palliative sedation was defined as "deliberately lowering a patient's level of consciousness in the final stage of life," and a symptom was considered refractory if "none of the conventional modes of treatment were effective or fast-acting enough, and/or if these modes of treatment were accompanied by unacceptable side-effects." It was clearly stated in the questionnaire that the study explicitly focused on CPS, defined as "sedation continued until death."

The questionnaire consisted of 38 closed-ended questions and six open questions and was divided into two parts. The first part included questions about the respondent's age, sex, years of clinical experience with end-of-life care (<5, 5–15, ≥16), whether they had at some time administered CPS (yes/no), and whether they were aware of the RDMA guideline on palliative sedation (yes/no). In addition, their knowledge of the contents of the guideline was assessed on a 5-point scale (poor to excellent). Each respondent was also asked about the number of patients who died in 2007 (0, 1–5, 6–10, 11–20, 21–50, >50) and the exact number of occasions on which CPS was administered in 2007. The second part addressed the practice of CPS in the most-recent case in 2007, with an explicit request to retrieve the information from the patient's medical file. This part included questions about the patient's age, sex, and primary disease (dementia, cancer, cardiovascular disease, pulmonary disease, nervous system disease, other diagnosis). When respondents filled in more than one primary diagnosis, it was registered as "multiple." In the questionnaire, no distinction was made between informed consent (yes/no) from the patient or the patient's legal representative. The indicating symptoms for CPS were pain, dyspnea, delirium, anxiety, vomiting, nausea, exhaustion, existential distress, loss of dignity, and other (more than one answer possible). The aim of CPS was defined as symptom relief, life shortening, or other (more than one answer possible). The respondents were asked whether a previous request for euthanasia had been reported. The physician judged the life expectancy before the start of CPS (1–4, 5–7, 8–14 , ≥15 days), and the duration of the CPS was defined in the exact number of days. In addition, whether the respondent expected a life-shortening effect of CPS (yes/no), whether CPS provided symptom relief according to the respondents

(4-point scale: no, hardly, partially, completely), and what the level of consciousness of the patient was at the time adequate symptom relief was attained from CPS (6-point scale: alert and orientated, drowsy, eyes closed follow directives, eyes closed responding to physical stimuli, eyes closed not responding to physical stimuli, disturbed brainstem function) was asked about. Respondents were also asked what the patient's intake was before the start of CPS (0, 1–500, 501–1,500, ≥1,501 mL) and whether they withheld, withdrew, started, or continued artificial hydration and feeding. To determine which medication was used to facilitate the start and continuation of CPS, the respondents were asked to fill in a maximum of three drugs, in order of rank, stating the starting and end dose (mg/24 h) and the route of administration.

Analysis

Descriptive analysis was performed using proportions for categorical variables and means ± standard deviations for continuous variables, using SPSS version 14.0.2 (SPSS, Inc,. Chicago, IL). The goodness-of-fit test was used to determine the representativeness of the registered nursing home physicians in the study of the total population of registered nursing home physicians. The duration of CPS was categorized, in categories similar to those used in the question to assess life expectancy before the start of CPS, for the analyses. To study the differences in the administration of CPS to patients with cancer and dementia, Pearson chi-square and Fisher exact tests were used. All P-values were two sided, and an alpha of .05 was considered to indicate statistical significance.

RESULTS

Respondents

Six hundred seventy-five of the 1,254 physicians returned the questionnaire (54% response rate) (Figure 1). In 2007, 28 respondents were not actively practicing and were excluded from the analysis, resulting in a study population of 647 respondents. For sex (P = .10; goodness-of-fit test) and age (P = .87; goodness of fit test), the respondents were representative of the total population of registered nursing home physicians. The majority of the respondents were women (65%). Mean age was 45 (range 25–65). Eighty percent of the nursing home physicians had more than 5 years of experience with palliative care, and 72% had at some time administered CPS. Almost all of them knew about the RDMA guideline on palliative sedation (98%). Fifty-two percent rated their level of knowledge about the contents of the guideline as good to excellent, and 12% rated their knowledge as moderate to poor (Table 1).

Forty-nine percent (n = 316) of the respondents indicated that they had used CPS in 2007; 307 of these provided information about the exact number of occasions on which CPS was administered in 2007 (9 missing); 60% (n = 185) administered CPS once or twice, and 22% (n = 69) administered CPS three to five times. One nursing home physician indicated that she had administered CPS to 30 patients in 2007. According to the data, a maximum of 15% of all patients who died in 2007 in the Netherlands and were treated by nursing home physicians received CPS.

Patients

Three hundred sixteen cases were described, mostly women (57%) of high age. The majority of the patients had cancer or dementia (Table 2). In all but one case, patient informed consent was obtained from the patient or the relative who was the patient's legal representative.

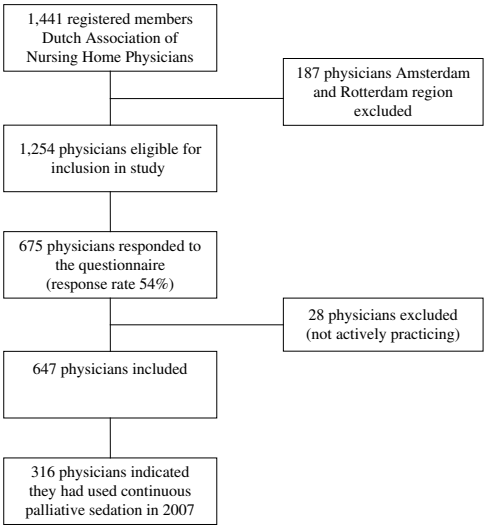


Figure 1. Flowchart of physicians throughout the study.

Table 1. Characteristics of Nursing Home Physicians (N = 647)

Characteristic	n (%)
Age	
25–39	189 (29)
40–54	339 (52)
55–65	118 (18)
Sex	
Female	419 (65)
Male	228 (35)
Experience, years	
<5	129 (20)
5–15	269 (42)
>15	247 (38)
Ever administered CPS	
No	184 (29)
Yes	461 (72)
Aware of guideline on palliative sedation	
No	12 (2)
Yes	634 (98)
Knowledge of contents of guideline	
Good to excellent	334 (52)
Reasonable	236 (37)
Moderate to poor	74 (12)

Data were missing for one physician on age and awareness of guideline on palliative sedation, for two physicians on experience and ever administered continuous palliative sedation (CPS), and for three physicians on knowledge of contents of guideline.

Characteristics of CPS

Eighty-two percent of patients were treated with CPS for two or more refractory symptoms, mostly pain, anxiety, exhaustion, or dyspnea (Table 3). If there was only one refractory symptom (n = 55), it was usually dyspnea (n = 16), pain (n = 12), or exhaustion (n = 10). In one case, existential distress was reported as the only refractory symptom. In 98% of cases, symptom relief was the aim of CPS. In 2% of cases, the co-intention was life shortening, whereas 1% (n = 2) had shortening of life as the sole intention. In 12% of cases, a previous request for euthanasia had been reported. In 94% of the patients, life expectancy was 7 days or less, and the duration of CPS was 7 days or less in 97% of the cases. The mean duration of the CPS was 2.8 days (median 2.0, range 0–21 days). Twenty-six percent of all physicians estimated that CPS had shortened life. According to the respondents, CPS provided complete symptom relief in 89% of the cases. At the time adequate symptom relief by CPS was attained, 47% of the patients had a level of consciousness varying from alert to responding to physical stimuli. Fifty-one percent of the patients were not responsive to physical stimuli, and 2% had a very deep level of unconsciousness, with disturbed brainstem function.

Hydration and Nutrition

Eighty-two percent of the patients had an intake of no more than 500 mL the day before CPS started, and 17% had no intake (Table 4). Three patients who received artificial hydration and nutrition had an intake of more than 1,500 mL a day. In 98% of cases, no artificial hydration was administered during CPS. In the group of patients who received artificial hydration before the start of CPS (n = 20), administration was discontinued in 15 and continued in five. Artificial hydration was started in one patient.

Table 2. Characteristics of Patients (N = 316)

Characteristic	n (%)
Age	
<41	1 (1)
41–60	32 (10)
61–80	142 (45)
>80	138 (44)
Sex	
Female	179 (57)
Male	134 (43)
Primary diagnosis	
Cancer	118 (38)
Dementia	63 (20)
Nervous system disease	39 (13)
Cardiovascular disease	32 (10)
Pulmonary disease	23 (7)
Multiple	23 (7)
Other	15 (5)

Data were missing for three patients on age, sex, and primary diagnosis.

Table 3. Characteristics of Continuous Palliative Sedation (CPS) (N = 316 Patients)

Characteristic	n (%)
Refractory symptom*	
Pain	164 (52)
Anxiety	139 (44)
Exhaustion	137 (44)
Dyspnea	124 (40)
Delirium	74 (24)
Loss of dignity	58 (18)
Existential distress†	50 (16)
Number of symptoms	
1	55 (18)
2	102 (32)
3	85 (27)
4	48 (15)
≥5	24 (8)
Intention‡	
Symptom relief	309 (98)
Life shortening	7 (2)
Request for euthanasia	
Yes	38 (12)
No	276 (88)
Life expectancy, days	
1–4	217 (69)
5–7	78 (25)
8–14	15 (5)
≥14	4 (1)
Duration of CPS, days	
1–4	266 (85)
5–7	36 (12)
8–14	8 (3)
≥14	2 (1)
CPS shortened life	
Yes	79 (26)
No	229 (74)
Effect of CPS	
Complete symptom relief	276 (89)
Partially symptom relief	34 (11)
Hardly any or no symptom relief	0 (0)
Level of consciousness at adequate symptom relief	
Alert and orientated	1 (0,3)
Drowsy	13 (4)
Eyes closed, following directives	10 (3)
Eyes closed, responding to physical stimuli	120 (39)
Eyes closed, not responding to physical stimuli	156 (51)
Disturbed brainstem function	7 (2)

* More than one refractory symptom possible; seven most frequently refractory symptoms shown.
† Measured using a dichotomous question. Existential distress is characterized according to the Royal Dutch Medical Association guideline as patients close to death with a range of severe physical complaints, where there is the feeling that one's existence is empty or meaningless and the distress cannot be alleviated by communication or spiritual support.
‡ More than one intention possible.
Data were missing for two patients on refractory symptom, request for euthanasia, and life expectancy; for four patients on duration of CPS; for six patients on effect CPS; for eight patients on expected shortened life; and for nine patients on level of consciousness at adequate symptom relief.

Table 4. Nutrition and Hydration (N = 316 Patients)

Nutrition and Hydration	n (%)
Intake before the start of CPS, mL	
0	53 (17)
1–500	201 (65)
501–1,500	52 (17)
>1,500	3 (1)
Artificial hydration	
Discontinued	15 (5)
Continued	5 (2)
Started	1 (0,3)
Not started	293 (93)
Artificial feeding	
Discontinued	12 (4)
Continued	6 (2)
Started	1 (0,3)
Not started	293 (94)

Data were missing for two patients on artificial hydration, four patients on artificial feeding, and six patients on intake before the start of continuous palliative sedation (CPS).

Drugs

To facilitate the start and continuation of CPS, 91% of the patients were administered midazolam, 64% received morphine, and 18% were prescribed haloperidol (Table 5). In 65% of cases, a combination of a benzodiazepine (midazolam, diazepam, clorazepate dipotassium, clonazepam) and an opioid (morphine, fentanyl) was prescribed, 30% were administered a benzodiazepine without an opioid, and 3% were prescribed an opioid without a benzodiazepine. With the exception of two patients, midazolam was administered subcutaneously. The mean starting dose of midazolam was 31 mg every 24 hours (median 30 mg/24 h), the mean end dose was 48 mg every 24 hours (median 30 mg/24 h). The dose range of midazolam at the start of sedation was 0 to 240 mg every 24 hours, and the dose range at the time of death was 0 to 480 mg every 24 hours. Two patients received a benzodiazepine other than midazolam at the start of sedation, which was changed to midazolam later on. In four patients, the administration of midazolam was ceased 24 hours or more before death. For morphine, which was given subcutaneously in all cases, the mean starting dose was 47 mg every 24 hours (median 30 mg/24 h), and the mean end dose was 65 mg every 24 hours (median 60 mg/24 h).

Table 5. Six Most-Frequently Used Drugs to Facilitate the Start and Continuation of Continuous Palliative Sedation

		mg/24/h, Mean ± Standard Deviation (Range)		
Drug	n (%)	Start Dose	End Dose	Administration (%)
Midazolam	289 (91)	30.6 ± 26.1 (0–240)	47.7 ± 56.8 (0–480)	Subcutaneous (99)
Morphine	201 (64)	47.5 ± 49.7 (0–600)	65.5 ± 64.7 (5–600)	Subcutaneous (100)
Haloperidol	57 (18)	6.3 ± 5.6 (1–30)	6.0 ± 6.6 (0–30)	Subcutaneous (93)
Levomepromazine	22 (7)	35.3 ± 36.8 (0–150)	50.8 ± 32.3 (8–150)	Subcutaneous (100)
Fentanyl	17 (5)	1.48 ± 0.98 (0.29–3.60)	1.58 ± 0.95 (0.29–3.60)	Transdermal (100)
Diazepam	13 (4)	25.4 ± 13.9 (10–60)	24.0 ± 20.1 (0–60)	Rectal (83)

Data were missing for nine patients.

Primary Disease

Comparing the administration of CPS to patients with cancer and dementia, there were only statistically significant differences between a previous request for euthanasia (cancer 17%, dementia 0%; $P < .001$, Fisher exact test), a life expectancy of 4 days or less before the start of the CPS (cancer 64%, dementia 78%; $P = .03$, Pearson chi-square test), and an absence of intake before the start of the CPS (cancer 11%, dementia 33%; $P = .001$, Pearson chi-square test). No statistically significant differences were found between patients with cancer or dementia in distribution of refractory symptoms, level of consciousness at the time adequate symptom relief was attained, or duration and effect of CPS (data not shown).

DISCUSSION

To the authors' knowledge, this is the first nationwide Dutch study to provide insight into the practice of CPS by nursing home physicians in a population of frail older adults with a high percentage of patients suffering from terminal cancer and dementia. The vast majority of Dutch nursing home physicians have experience with administering CPS at some time. In 2007, most patients were elderly women and had two or more refractory symptoms. The most frequent of these were pain, anxiety, exhaustion, and dyspnea. In almost all cases, symptom relief was the aim, and in 12% of cases, a previous request for euthanasia had been reported. Life expectancy and duration of the CPS were 7 days or less in almost all patients. In general, nursing home physicians judged CPS to be effective in relieving refractory symptoms.

More than half of the patients were unresponsive to physical stimuli at the time adequate symptom relief was attained and must be qualified as being in deep and continuous sedation. For 82% of patients, intake was less than 500 mL before the start of CPS, and in most cases artificial hydration was withheld during CPS. Midazolam was the most frequently used drug. The administration of CPS to patients with cancer and dementia differed significantly with respect to the following factors: previously made request for euthanasia, life expectancy of 4 days or less, and absence of intake before the start of CPS.

Care should be taken when comparing the figures of this study with the results of previous international studies. First, this study did not include temporary or intermittent palliative sedation, and the questionnaire used the term "continuous palliative sedation." Most studies performed over the past decade have focused on continuous deep sedation, [5–9,11–13,17–30] which covers just 53% of the cases in the current study. Second, the Netherlands is the only country where nursing home medicine exists as an independent medical specialism with its own specific training program.[31] In other countries, general practitioners or other physicians take care of these patients. Within these constraints, some of the results of the current study will be compared here with those of previous studies.

The distribution of symptoms considered refractory in this study is in line with previous studies,[7–9,11–13] although the current study found a higher frequency of loss of dignity (18% vs 6.5%) and exhaustion (44% vs 13%) and a lower frequency of anxiety (44% vs 65.2%).[9] The RDMA guideline explicitly mentions exhaustion as a contributor to refractory suffering because its presence may exacerbate suffering, and it is a determining factor of the patient's endurance. This may lead to the conclusion that palliative sedation is the only reasonable option left.[3] Furthermore, little is known about the pathogenesis of exhaustion, so conventional modes of treatment may be less successful than treatments for other symptoms at the end of life.[32]

The presence of loss of dignity and existential distress is consistent with previous research, although some authors have questioned whether viewing existential suffering as a symptom or a medical state is justified,[33] but given the involvement of physicians with dying patients, existential distress cannot be separated from the domain of medicine and can therefore be a part of the indication for palliative sedation. The RDMA guideline does not define this state but instead describes or characterizes it in the text: "In such cases, this existential suffering cannot be alleviated by communication or spiritual support. These patients have often been through a great deal of distress, are often extremely ill and weak, close to death, and have a range of physical complaints, some of them often severe. The patient's body has reached its end, literally and figuratively, and everything that needed saying has been said and there is the feeling that one's existence is empty or meaningless (existential suffering)."[3]

In a retrospective study, it is not possible to determine the precise reason for the patient's existential suffering. Despite the vagueness of the term, existential suffering often proves to be an important reason for discussing end-of-life decisions. A prospective study to determine exactly what happens in these cases would be worthwhile.

In 2004, it was reported that 59% of all nursing home physicians performed continuous deep palliative sedation with the (co)intention of hastening death.[11] The current study found a considerably lower percentage (2%). In 12% of all cases, and 17% of patients with cancer, a previous request for euthanasia had been reported. These percentages are higher than found in previous research in nursing home populations, with percentages of 6.5% and 9% found.[7,9] This might indicate that CPS is used as an alternative to euthanasia in some cases. Why a euthanasia request was not granted in such cases needs to be investigated.

Whether artificial nutrition and hydration should be forgone in CPS is a subject of ongoing debate. In other European countries, continuous deep sedation in nursing homes and residential homes is frequently administered with artificial nutrition and hydration.[23] The current study shows that nursing home physicians in the Netherlands mostly do not administer artificial fluids. The minimal intake before sedation in the vast majority of the study population could be a contributing factor in this decision by nursing home physicians. It could be argued that artificial hydration is medically futile, hampers the natural dying process, and may result in additional suffering, whereas withholding artificial hydration will not influence survival.

The general consensus is that midazolam is the drug of choice for inducing CPS because of its fast onset of action, the ease of titration, and the option of rapid reversibility. Morphine is not considered to be a suitable drug for inducing CPS.[3,4,16] The current study revealed a higher frequency of a benzodiazepines being used to induce and maintain CPS than previous nursing home physician studies (95% vs 75–89%) and found a lower frequency of an opioid without a benzodiazepine being used for this purpose (3% vs 10–26%).[7,11,12] This shift is probably because of the publication of the RDMA guideline, as well as media attention to the issue and the ongoing debate among physicians. Despite these changes in practice, it was found that nursing home physicians increased the mean dose of morphine during CPS. Morphine is usually continued as a symptom-directed treatment, but benzodiazepines are administrated to induce sedation.[13,34] The reason of the increase of the morphine dosages is unclear.

Almost all other studies show smaller dose ranges, with a lower maximum dose of midazolam than in the current study,[18,19,24,35–44] although the mean dose of midazolam used in the current study was lower than or similar to that in most other studies.[18,19,24,35–37,39–41,43,45,46] Furthermore, only nine patients received an end dose of midazolam greater than 120 mg every 24 hours, and the dose range was consistent with the recommendations of the RDMA guideline. Moreover, continuous deep palliative sedation was administered in only 53% of cases, suggesting that the doses used were proportional to patients' needs, although little is known about the pharmacokinetics of midazolam in a frail, elderly population. Further research is needed to support the medication recommendations of the RDMA guideline.

Despite the specific pathophysiology and symptomatology of each primary underlying disease, no statistically significant differences were found between the distribution of refractory symptoms in patients with cancer and dementia. In addition, no statistically significant differences were found in outcomes of CPS, such as symptom relief and duration.

There was a statistically shorter life expectancy in terminally ill patients with dementia than in patients with cancer before the start of CPS. The fact that more patients with dementia had no intake before the start of CPS might have helped the physician to determine that death would ensue within 1 or 2 weeks. In addition, it suggests that whether nutrition or hydration will be withheld during CPS is discussed more frequently for patients with cancer than for those with dementia.

This is the first nationwide study of the practice of CPS by Dutch nursing home physicians. Nevertheless, these findings should be interpreted within the constraints of a questionnaire study. First, there were limitations with respect to the study population. Although the respondents were representative regarding sex and age of the total population of registered nursing home physicians, a portion of nursing home physicians in the Amsterdam and Rotterdam regions were excluded, and the response rate was only 54%. Possible differences between respondents and nonrespondents, as well as the excluded physicians in the Amsterdam and Rotterdam regions, with respect to the practice of CPS cannot be excluded.

Second, although clear definitions of palliative sedation and refractory symptoms in the questionnaire were used, items such as loss of dignity and existential distress were not defined. Also primary disease was not defined using, for example, the International Classification of Diseases. Third, refractoriness of suffering was not determined by investigating the etiology of each type of suffering, what types of treatment had been attempted before sedation, and how symptoms were recognized, especially in patients with dementia. Fourth, respondents may have had difficulty recalling patient characteristics, although recall bias was probably limited because of the instruction to use data extracted from the medical file.

This study shows that, in addition to physical symptoms, nursing home physicians often mention anxiety, exhaustion, loss of dignity, and existential distress as refractory symptoms in the decision to start CPS. Furthermore, close to one in five patients with cancer had made a previous request for euthanasia. The dosage range of midazolam in this study fits the recommendations of the Dutch national guideline on palliative sedation, although international studies show smaller dosage ranges. Further prospective research about the acceptability and assessment of nonphysical symptoms as indications for CPS and the optimal medication scheme for CPS in frail elderly patients is recommended. Finally, adequate palliative care with careful assessment of potential reversible factors and nonsedating alternatives should be the keystone of treatment before starting palliative sedation.

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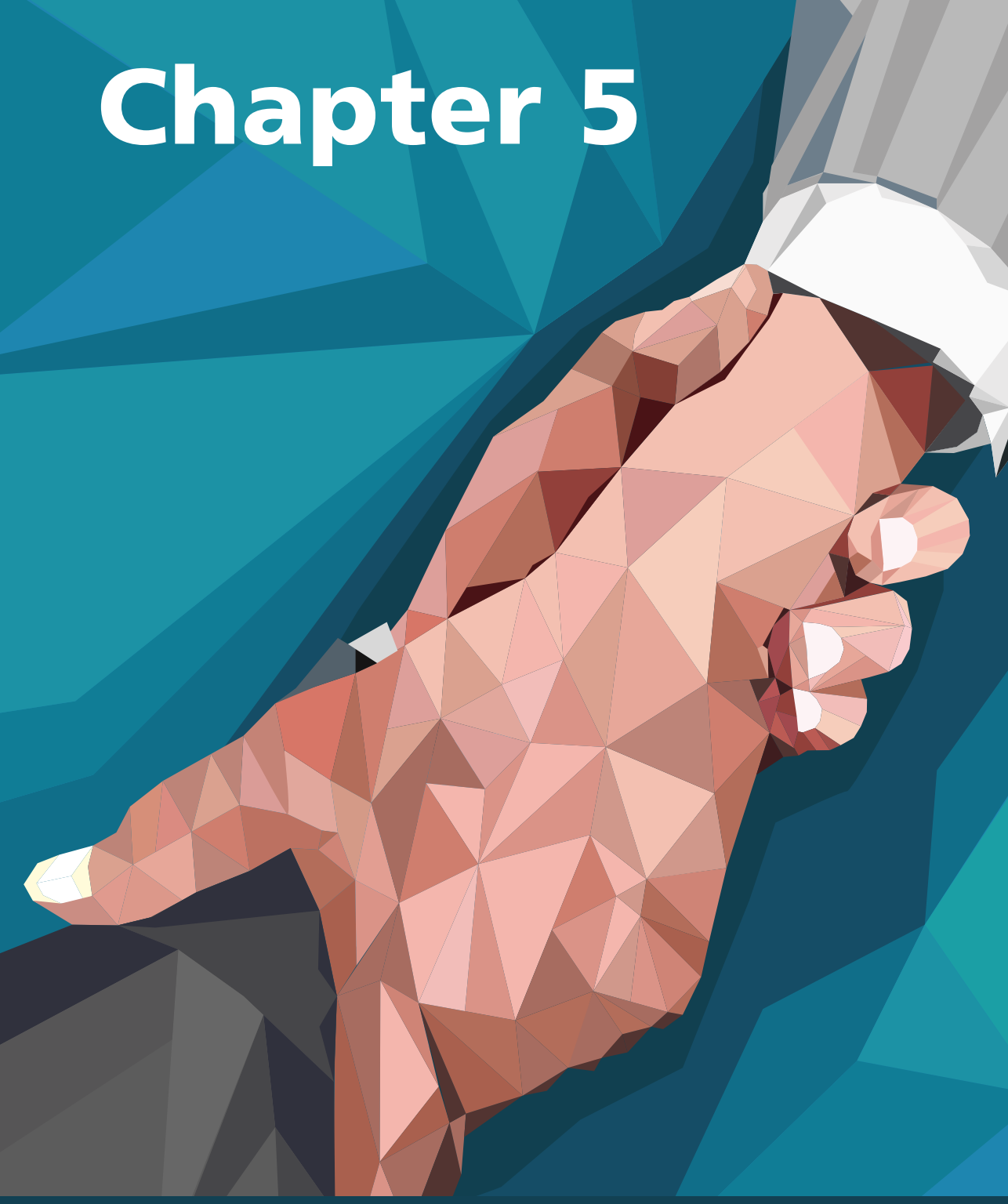
Chapter 5



The practice of continuous palliative sedation in long-term care for frail patients with existential suffering.

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Chapter 5

Abstract

Some guidelines and recommendations identify existential suffering as a potential refractory symptom for which continuous palliative sedation (CPS) can be administered under certain conditions. However, there has been little research on the characteristics of patients with existential suffering treated with CPS and the degree to which the preconditions are fulfilled. The aim of this study was to provide insight into this specific indication for CPS. Questionnaires were sent to nursing home physicians in the Netherlands, who described 314 patients. Existential suffering was a refractory symptom in 83 of the patients. For most of the patients with refractory existential suffering, other refractory symptoms were also reported, and life expectancy was seven days or less; informed consent for initiating CPS had been obtained in all cases. Consultation and intermittent sedation before the start of CPS were far less frequently reported than one would expect based on the guidelines. Multivariate analysis showed that being male, having previously requested euthanasia, having a nervous system disease, or having an other diagnosis were positively correlated with the administration of CPS for existential suffering. We conclude that more attention should be paid to the suggested preconditions and to the presence of existential suffering in male patients or patients with a nervous system disease.

Chapter 5

INTRODUCTION

When patients with a terminal disease experience refractory symptoms — that is, symptoms that do not respond to conventional therapies, despite intensive efforts, or that cannot be controlled without causing intolerable side effects[1] — an indication arises for palliative sedation. Palliative sedation has been defined as "the deliberate lowering of a patient's level of consciousness in the last stage of life",[1] and it is considered an ethically acceptable therapy for patients with refractory symptoms.[1-4] The term "palliative sedation" encompasses two distinct types of intervention: brief or intermittent sedation, and continuous palliative sedation (CPS) administered until death.[1] Although both represent stages in the ongoing process of providing proportional sedation for refractory symptoms, the distinction is made to emphasize the fact that CPS is only to be administered to patients who are near death.[1] There is sometimes a lack of clarity regarding the difference between CPS and euthanasia, and it has been suggested that some physicians view CPS as a way of avoiding euthanasia.[1] However, both the European Association for Palliative Care Ethics Task Force[5] and the Royal Dutch Medical Association[1] have clearly stated that CPS is a medical intervention and is totally different from euthanasia in its aim, procedure, and result.

The most common indications for administering palliative sedation are delirium, dyspnea, and pain. Palliative sedation is also sometimes used to treat existential suffering.[6,7] Definitions of existential suffering at the end of life include: loss of a sense of personal meaning; loss of a sense of life's purpose; fear of death; feelings of despair, anguish, and hopelessness; perception of being a burden to others; loss of dignity; sense of helplessness; and sense of betrayal.[8] In the palliative care community, there is still a lack of consensus on a definition of existential suffering. Furthermore, although existential suffering is considered to be a condition that medical practitioners must address,[9] there is no general consensus on whether palliative sedation is an appropriate intervention for it.[10] Existential suffering may occur long before the terminal phase.[2,11] It tends not to be progressive in the sense that suffering caused by physical symptoms is (it often fluctuates), and psychological adaptation and coping are common.[2,11] Also, it is difficult for practitioners to determine whether a patient's existential suffering is refractory[2,11,12] and to distinguish it from treatable psychiatric conditions such as depression.[12] This may cause them to administer CPS in cases where other, more conventional therapies would be more appropriate. Although interventions for existential suffering are not well established,[2,11,12] the American Medical Association (AMA) contends that existential suffering is better addressed through interventions other than palliative sedation.[13] Despite the AMA's position on this issue, some guidelines and recommendations identify existential suffering as a potential refractory symptom that can be treated with CPS under specific conditions. These preconditions include: an expert in psychosocial problems and meaning-of-life issues has been consulted;[1-4,14-16] intermittent sedation is initiated before CPS is attempted;[2,16] the patient has a life expectancy of a maximum of one to two weeks;[1,14,15] informed consent has been obtained;[14] and existential suffering is not the patient's sole refractory symptom.[1]

Most patient-based studies focus on the frequency of existential suffering as an indication for CPS,[17-32] but little insight has been achieved into the characteristics of patients with existential suffering treated with CPS and the degree to which the preconditions have been fulfilled. A few studies have focused on

the use of palliative sedation for existential suffering. Morita investigated the use of palliative sedation to relieve psychoexistential suffering in 90 terminally ill cancer patients in palliative care units in Japan.[33] The condition of these patients was generally poor, and their suffering was refractory, despite the fact that they were receiving intermittent sedation and specialized psychiatric, psychological, and/or religious counselling. CPS was administered to them on the basis of informed consent. In another study, by Morita et al., data of previous studies was reanalyzed in order to clarify the physical conditions of 20 terminally ill cancer patients with existential suffering who received sedation in a palliative care unit.[34] Most of these patients were in extremely poor physical condition just before sedation: 95 percent had a Palliative Performance Scale score under 40, could take nourishment orally only by mouthfuls or less, and had a predicted survival time of three weeks or less. One patient received sedation for existential suffering alone. Anquinet et al. interviewed 35 physicians involved in caring for cancer patients with psychological and existential suffering who had been continuously sedated until they died.[35] The physicians reported that they had attempted an array of pharmacological and psychological interventions, which were ultimately ineffective or inappropriate, to relieve the patients' suffering before applying CPS. Reported preconditions for administering sedation were the presence of refractory physical symptoms, a short life expectancy, and the patient's explicit request for sedation.

Furthermore, little is known about which patient characteristics are correlated with the administration of CPS for existential suffering. Knowledge of such characteristics could help physicians and other healthcare professionals to identify patients at risk of developing refractory existential suffering and thereby facilitate early referral to a psychotherapist, social worker, or spiritual counsellor, possibly precluding the need for CPS.

The aim of this study was therefore to provide greater insight into the characteristics of patients with existential suffering who are treated with CPS and the degree to which the preconditions for administering CPS are fulfilled.

METHODS

Study Design and Data Collection

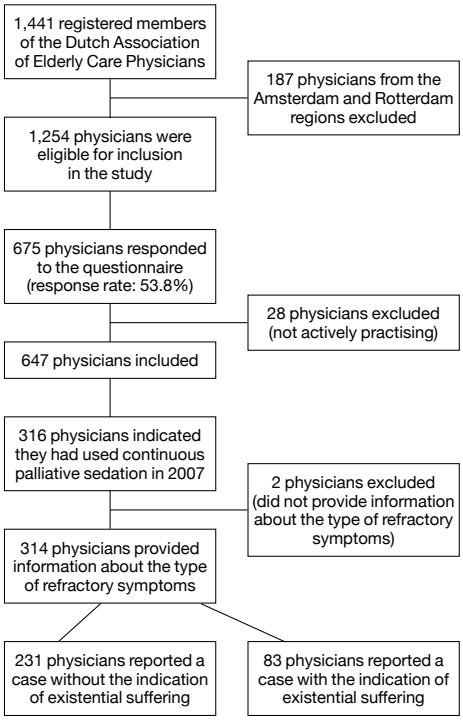
A structured retrospective questionnaire was sent to 1,254 nursing home physicians in February 2008.[36] All registered members of the Dutch Association of Elderly Care Physicians were eligible for the study (n=1,441), except 187 of the 292 members in the Amsterdam and Rotterdam regions — they were excluded due to their involvement in a parallel, ongoing study on palliative sedation that was being conducted in these regions. Only anonymous data were collected. A reminder to return the questionnaire was sent after three weeks. Data collection ended in May 2008.

Questionnaire

In the questionnaire, CPS was defined as "the deliberate lowering of a patient's level of consciousness in the last stage of life, continued until the time of death." The questionnaire consisted of 38 closed-ended questions and six open-ended questions and was divided into two parts. The first part contained 13 questions about the characteristics of the respondent — for example, age, sex, and years of clinical experience with end-of-life care. The second part contained questions about the respondent's most recent case involving CPS within the previous 12 months and an explicit request to retrieve information from patients' medical files; this part also included questions about the patient's age, sex, and primary

diagnosis (dementia, cancer, cardiovascular disease, pulmonary disease, nervous system disease, or other diagnosis). When respondents listed more than one primary diagnosis, it was registered as "multiple." Respondents were asked whether a previous request for euthanasia had been reported, whether they had considered intermittent sedation before commencing CPS, and whether they had discussed alternative strategies with another professional (a physician, nurse, palliative care consultant, spiritual counsellor, other, or nobody) before deciding to start CPS. In the questionnaire, no distinction was made between informed consent given by the patient or by the patient's legal representative. The indicating symptoms for CPS were pain, dyspnea, delirium, anxiety, vomiting, nausea, exhaustion, existential suffering, loss of dignity, and other (it was possible to provide more than one answer). Respondents were asked to explain their purpose in initiating CPS by selecting one or more of these options: symptom relief, life shortening, or other. They were also requested to record patients' life expectancy before the start of CPS (1 to 4 days, 5 to 7 days, 8 to 14 days, and 15 days or more); CPS duration was to be expressed as an exact number of days. In addition, respondents were asked whether CPS delivered symptom relief (on a 4-point scale: no, hardly, partially, or completely), and what the patient's level of consciousness was at the time adequate symptom relief was achieved (on a 6-point scale: alert and oriented; drowsy; eyes closed, following directives; eyes closed, responding to physical stimuli; eyes closed, not responding to physical stimuli; or disturbed brainstem function). Then they were asked to describe the patient's intake before the start of CPS (0, 1 to 500, 501 to 1,500, ≥1,501 mL) and to note whether they had withheld, withdrawn, started, or continued artificial hydration and feeding. Finally, respondents were asked to list a maximum of three drugs they used for CPS, and to state the starting and end dose (mg/24 h) and route of administration.

Figure 1 / Flowchart of Physicians throughout the Study



Analysis

This study involved a subanalysis of a previously published study,[36] and focused on refractory existential suffering. For this study, patients with existential suffering were defined as those for whom the respondent had filled in the tick box for existential suffering and/or loss of dignity as a refractory symptom.

A descriptive analysis was performed using proportions for categorical variables and means and standard deviations for continuous variables. Patient age was categorized as: younger than 51, 51 to 80, and 81 years and older. The duration of CPS was categorized as: 1 to 4, 5 to 7, 8 to 14, and more than 14 days. To analyze the correlation between characteristics of patients with existential suffering and the administration of CPS, gender, age, dementia, cancer, cardiovascular disease, pulmonary disease, nervous system disease, other diagnoses, multiple diagnoses, and previous requests for euthanasia were analyzed as independent variables using Pearson's chi-squared test. Using the aforementioned independent variables, multiple logistic regression models were constructed to analyze the probability of patients with existential suffering being sedated. Data are reported with odds ratios (OR) and 95 percent confidence intervals (95 percent CI). All p-values were tested as two-sided, and an alpha value of .05 was considered to indicate statistical significance. Statistical analyses were performed using the SPSS 20.0 (IBM Corp., 2011).

RESULTS

A total of 675 physicians returned the questionnaire (a 53.8 percent response rate). We excluded 331 respondents because they had not administered CPS in the past year, and 28 because they were not actively practising. Of the remaining 316 respondents, we excluded 2 because they did not provide information about the type of refractory symptoms they had encountered among their patients. The final sample consisted of data describing the cases of 314 patients receiving CPS. Of these, 83 patients (26.4 percent) who had received CPS for existential suffering were identified. In this group, 1 patient (1.2 percent) receiving CPS had existential suffering as a sole refractory symptom. For 73 patients (88.0 percent), existential suffering coexisted with one to four other refractory symptoms; 9 patients (10.8 percent) had five to seven other refractory symptoms. Among those patients who did not report existential suffering (n=231), 54 (23.4 percent) had one refractory symptom and 177 (76.6 percent) had two to five refractory symptoms.

Characteristics before the Administration of CPS

The day before the patients with existential suffering had commenced CPS, 80.5 percent of them had received oral intake or artificial hydration of 500 mL or less. Intermittent sedation was considered in 40.2 percent of cases. In 4.8 percent of cases, the attending physician consulted a spiritual counsellor, and in 8.4 percent of cases, a palliative care consultant was called upon. For all patients receiving CPS for existential suffering, informed consent was obtained for the administration of CPS. Life shortening was the physician's rationale for CPS in 6.0 percent of cases. For 90.4 percent of the patients, life expectancy at the start of CPS was seven days or less (Table 1).

Characteristics during the Administration of CPS

For all but three patients with refractory existential suffering, no artificial hydration was administered during CPS. At the time adequate symptom relief was obtained, 60.7 percent of the patients were not responsive to physical stimuli. The mean end dose of midazolam, the most frequently used drug for CPS,

was 46.1 mg every 24 hours. For 96.4 percent of the patients, the duration of CPS was seven days or less. According to the respondents, CPS provided complete symp tom relief in 92.5 percent of cases (Table 2).

Correlation between Patient Characteristics and CPS

Univariate analysis revealed that patients sedated for existential suffering were more likely to be male (p=0.01) and to have been diagnosed with nervous system disease (p<0.01) or other condition (for example, cachexia, anxiety, aspiration pneumonia, renal failure, ileus, or fracture) (p=0.04); they were also more likely to have requested euthanasia (p<0.01) (Table 3).

Multivariate logistic regression analysis showed that the nature of the underlying disease was significantly correlated with the administration of CPS for existential suffering (p<0.01). Having a nervous system disease (OR: 3.64; 95 percent CI: 1.64-8.06) (p<0.01) or an "other diagnosis" (OR: 4.61; 95 percent CI: 1.34-15.81) (p=0.02) were positively correlated with the administration of CPS for existential suffering as compared to having cancer. Moreover, multivariate analysis showed that certain patient characteristics were correlated with the administration of CPS for existential suffering: being male (OR: 1.91; 95 percent CI: 1.11-3.28) (p=0.02); and having requested euthanasia (OR: 2.93; 95 percent CI: 1.37-6.26) (p=0.01) (Table 4).

Table 1 / **Characteristics before the Administration of Continuous Palliative Sedation (CPS) for Patients with Existential Suffering (n=83)**[a]

Characteristic	Indication of existential suffering No. (%)
Intake before the start of CPS, mL	
0	11 (13.4)
1-500	55 (67.1)
501-1,500	15 (18.3)
>1,500	1 (1.2)
Intermittent sedation considered	
No	49 (59.8)
Yes	33 (40.2)
Informed consent	
No	0 (0)
Yes	81 (100)
Consultation with palliative care consultant	
No	76 (91.6)
Yes	7 (8.4)
Consultation with spiritual counsellor	
No	79 (95.2)
Yes	4 (4.8)
Intention of the physician[b]	
Symptom relief	80 (96.4)
Life shortening	5 (6.0)
Life expectancy, days	
1-4	53 (63.9)
5-7	22 (26.5)
8-14	5 (6.0)
>14	3 (3.6)

[a] Data were missing for one patient on "Intake before the start of CPS" and "Intermittent sedation considered"; for two patients on "Informed consent."
[b] More than one intention was possible.

Table 2 / **Characteristics during the Administration of Continuous Palliative Sedation (CPS) for Patients with Existential Suffering (n=83)**[a]

Characteristic	Indication of existential suffering No. (%)
Artificial hydration[b]	
Discontinued	2 (2.4)
Continued	3 (3.7)
Started	0 (0)
Not started	77 (93.9)
Level of consciousness at adequate symptom relief[b]	
Alert and oriented	0 (0)
Drowsy	3 (3.8)
Eyes closed, following directives	4 (5.1)
Eyes closed, responding to physical stimuli	24 (30.4)
Eyes closed, not responding to physical stimuli	46 (58.2)
Disturbed brainstem function	2 (2.5)
Duration of CPS, days[b]	
1-4	76 (91.6)
5-7	4 (4.8)
8-14	3 (3.6)
>14	0 (0)
Effect of CPS[b]	
Complete symptom relief	74 (92.5)
Partial symptom relief	6 (7.5)
Hardly any or no symptom relief	0 (0)
Midazolam initial dose, mg/24 h[c]	28.6 (18.6)[d]
Midazolam final dose, mg/24 h[c]	46.1 (60.8)[d]

[a] Data were missing for one patient on "Artificial hydration"; for three patients on "Effect of CPS"; for four patients on "Level of consciousness at adequate symptom relief"; for eight patients on "Midazolam initial dose"; and for 12 patients on "Midazolam final dose."
[b] Data are given as a number (percentage).
[c] Data are given in mean (standard deviation).
[d] Administration routes were subcutaneous, except for one, which was intramuscular.

Table 3 / **Patient Characteristics with and without Existential Suffering as a Reported Indication for Continuous Palliative Sedation**

Characteristic[a]	With indication of existential suffering (n=83) No. (%)	Without indication of existential suffering (n=231) No. (%)	p-value[b]
Age			
<51 years	3 (3.6)	9 (3.9)	0.58
51-80 years	47 (56.6)	114 (50.0)	
>80 years	33 (39.8)	105 (46.1)	
Gender			
Male	45 (54.2)	87 (38.2)	**0.01**
Female	38 (45.8)	141 (61.8)	
Dementia			
No dementia	71 (86.6)	177 (77.3)	0.07
Dementia	11 (13.4)	52 (22.7)	
Cancer			
No cancer	54 (65.9)	140 (61.1)	0.45
Cancer	28 (34.1)	89 (38.9)	
Cardiovascular disease			
No cardiovascular disease	76 (92.7)	203 (88.6)	0.30
Cardiovascular disease	6 (7.3)	26 (11.4)	
Pulmonary disease			
No pulmonary disease	77 (93.9)	211 (92.1)	0.60
Pulmonary disease	5 (6.1)	18 (7.9)	
Nervous system disease			
No nervous system disease	62 (75.6)	210 (91.7)	**<0.01**
Nervous system disease	20 (24.4)	19 (8.3)	
Other diagnosis			
No other diagnosis	75 (91.5)	222 (96.9)	**0.04**
Other diagnosis	7 (8.5)	7 (3.1)	
Multiple diagnoses			
No multiple diagnoses	77 (93.9)	211 (92.1)	0.60
Multiple diagnoses	5 (6.1)	18 (7.9)	
Previous request for euthanasia			
No previous request	64 (78.0)	210 (91.3)	**<0.01**
Previous request	18 (22.0)	20 (8.7)	

[a] Data were missing for three patients on "Age," "Gender," "Dementia," "Cancer," "Cardiovascular disease," "Pulmonary disease," "Nervous system disease," "Other diagnosis," and "multiple diagnoses"; for "two patients on "Previous request for euthanasia."
[b] Pearson's chi-squared test; significant p-values are shown in boldface.

Table 4 / **A Multiple Logistic Regression: Patient Characteristics Correlated with the Administration of Continuous Palliative Sedation for Existential Suffering (n=307)**

Determinant	Direction (reference)	OR[a]	95% CI[b]	p-value[c]
Gender	Male (female)	1.91	1.11 – 3.28	**0.02**
Age	<51 years (>80 years)	0.66	0.14 – 3.06	0.59
Age	51-80 years (>80 years)	1.24	0.69 – 2.25	0.48
Dementia	Present (cancer)	0.89	0.38 – 2.08	0.79
Cardiovascular disease	Present (cancer)	0.82	0.29 – 2.31	0.71
Pulmonary disease	Present (cancer)	0.94	0.31 – 2.91	0.92
Nervous system disease	Present (cancer)	3.64	1.64 – 8.06	**<0.01**
Other diagnosis	Present (cancer)	4.61	1.34 – 15.81	**0.02**
Multiple diagnoses	Present (cancer)	0.88	0.28 – 2.75	0.83
Previous request for euthanasia	Present (not present)	2.93	1.37 – 6.26	**0.01**

[a] Odds ratio.
[b] Confidence interval.
[c] Significant p-values are shown in boldface.

DISCUSSION

This study provides insight into the practice of administering CPS to treat existential suffering. In almost all of the patients reported on in the study, existential suffering coexisted with refractory physical symptoms, and life expectancy was seven days or less. In all cases, informed consent for the administration of CPS had been obtained from either the patient or the patient's legal representative. Intermittent sedation and consultation before commencing CPS were less frequently reported. Having a nervous system disease or "other diagnosis" was positively correlated with receiving CPS for existential suffering compared to having cancer. Moreover, the multivariate analysis showed that being male or having requested euthanasia were positively correlated with receiving CPS for existential suffering.

Some guidelines and recommendations describe specific preconditions for offering CPS for existential suffering.[1-4,14-16] The results of this study related to the presence of physical symptoms in patients with existential suffering, informed consent, and limited life expectancy are generally in line with these preconditions. However, the use of intermittent sedation and consultation with a palliative care consultant or spiritual counsellor before starting CPS were far less frequently reported than one would expect, given the guidelines. Applying intermittent sedation before administering CPS would allow patients a time out and give healthcare providers a chance to reassess, possibly preventing a vicious cycle of existential suffering.[11] Although physicians are generally aware of the importance of recognizing and treating existential suffering at the end of life, this is not always included in advance care planning and training programs. Routine consultation with experts in the fields of psychology, psychiatry, or spirituality/religion is therefore recommended in such cases.[37] In the Netherlands, the Comprehensive Cancer Centre has established a national network of consultation teams specializing in palliative care services.

Our multivariate analysis showed that some patient characteristics were positively correlated with the administration of CPS for existential suffering. In our questionnaire, we didn't ask the respondents to specify the category nervous system disease in terms of precise diagnosis. This category could include rapidly progressive diseases of the nervous system, like amyotrophic lateral sclerosis. With such diseases, the fear that symptoms experienced today will be worse tomorrow can induce hopelessness and existential distress.[38] In focusing intently on treating the physical symptoms of the disease, physicians might fail to attend to existential suffering. Regarding the questionnaire category "other diagnosis," the diversity of the diagnoses reported by respondents and the limited number of cases involved makes it more difficult to identify a clear correlation with the administration of CPS for existential suffering. A possible explanation for male gender being positively correlated with initiation of CPS is that psychosocial and spiritual care has a more emotional orientation and is thus, perhaps, a less appropriate and effective approach to take with male patients.[39] The positive correlation of a euthanasia request with the decision to commence CPS may suggest that such a request places the patient with existential suffering on a slippery slope toward CPS —physicians could be opting to apply CPS even in cases were euthanasia would be more appropriate. However, careful interpretation is warranted. We did not ask physicians why a previous request for euthanasia was not granted. There could be plausible reasons for denying such a request. For example, it might not have been possible to arrange a consultation with an independent physician because the patient was dying very quickly; thus, one of the legal criteria allowing for euthanasia could not be met. Furthermore, some of our findings — such as the dose of midazolam administered and level of consciousness at adequate symptom relief — point to a proportional use of CPS and do not reflect an intention on the part of the physician to hasten death. Other findings, however, could indicate the presence

of an intention to hasten death, as some respondents reported a co-intention of life shortening. Also, no artificial hydration was administered for some patients during CPS, despite their intake of more than 500 mL before the start of CPS. Although suspending artificial nutrition and hydration during administration of CPS conforms to the Dutch guideline,[1] such patients are likely to die sooner as a result of dehydration, and an intention of life shortening could therefore be present.

LIMITATIONS

Several limitations of this study warrant attention. First, there is no clear, accepted operational definition of "existential suffering," which has given rise to the risk of physicians making inconsistent diagnoses; this could have biased the validity of our results. Also, we merged the refractory symptoms of existential suffering and loss of dignity, as loss of dignity is mentioned in the literature as part of existential suffering;[8] however, we did not include exhaustion, which, besides being a physical pathogenesis, can also have an existential aspect. Second, in almost all patients, refractory existential suffering coexisted with other refractory physical symptoms. In this study, we could not determine what impact existential suffering had on the decision to administer CPS, whether this suffering was truly refractory, or whether treatment of it really could have reduced the need for CPS. However, other research has shown that among patients starting CPS, a refractory state can be the result of multiple symptoms.[26,29,40-42] In such cases, the initiation of CPS tends to arise from a clinical situation in which physical and nonphysical symptoms interact to create a refractory state.[1,40] Timely interventions could stop this cascade of symptoms and prevent a refractory state from developing. Third, although our respondents were representative of the gender and age of the total registered nursing home physician population,[36] the response rate was 53.8 percent; nonresponse bias may therefore have influenced our results. Also, a portion of the nursing home physicians in the Amsterdam and Rotterdam regions were excluded from participation, and, due to the design of the study, recall bias could be present. Fourth, this is an explorative study, which decreases model robustness. Finally, since existential suffering can be influenced by cultural factors, the findings of this study might not be generalizable to other countries or ethnic groups.

CONCLUSION AND RECOMMENDATIONS

Although an awareness of and respect for the needs of patients with existential suffering is an essential part of medical care, the use of CPS for existential suffering should be approached with caution, and such treatment should be offered in compliance with the preconditions laid out in the relevant guidelines and recommendations. Preconditions such as consultation with an expert in psychosocial problems and meaning-of-life issues, and administration of intermittent sedation before the start of CPS, deserve more attention. Furthermore, this study shows that greater attention needs to be paid to the existential suffering experienced by patients, especially male patients and those with a nervous system disease. Appropriate interventions for these patients could alter the course of their symptoms, and consequently their need for CPS. Among patients receiving CPS, refractory existential suffering nearly always occurs in conjunction with refractory physical symptoms. Further research is therefore needed to determine how existential suffering affects or is affected by other symptoms patients may be experiencing, and prospective research should be undertaken to clarify the impact of existential suffering on the decision to administer CPS. Such research could also illuminate the reasons behind decisions not to grant requests for euthanasia. Finally, we need to develop a consistent definition of existential suffering in the literature, as the lack of consensus on such a definition further hinders discussion and research efforts.

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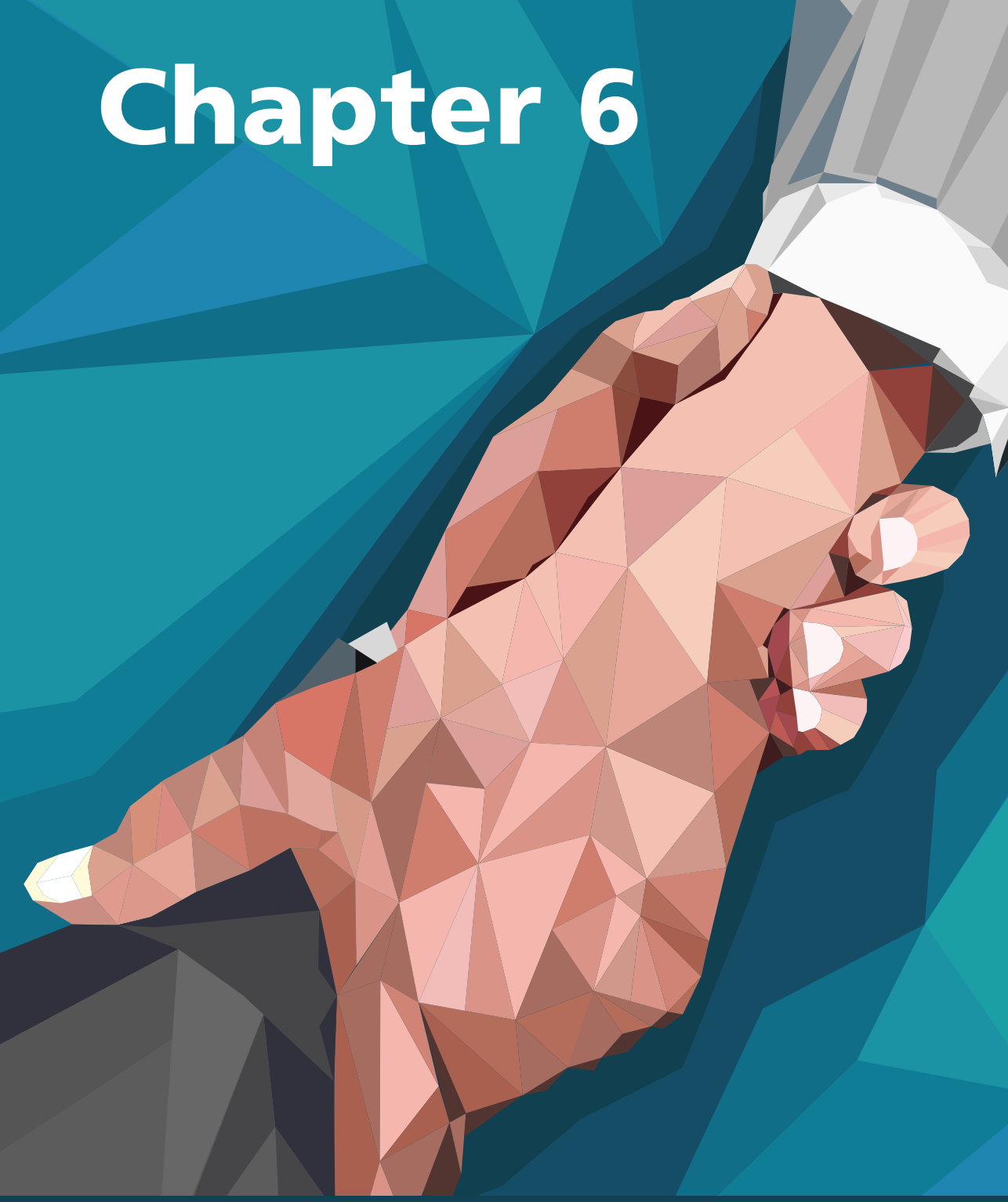
Chapter 6



Level of discomfort decreases after the administration of continuous palliative sedation: a prospective multicenter study in hospices and palliative care units.

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Abstract

Context.
A gold standard or validated tool for monitoring the level of discomfort during continuous palliative sedation (CPS) is lacking. Therefore, little is known about the course of discomfort in sedated patients, the efficacy of CPS, and the determinants of discomfort during CPS.

Objectives.
To identify the course of discomfort in patients receiving CPS.

Methods.
A prospective observational multicenter study in nine hospices and palliative care units was performed. The Discomfort Scale-Dementia of Alzheimer Type (DS-DAT) was independently assessed for monitoring of patient discomfort during CPS. The DS-DAT scores range from 0 (no observed discomfort) to a maximum of 27 (high level of observed discomfort). Using a mixed model, the mean group score of discomfort between four predefined time frames of CPS was compared, correcting for confounding patient characteristics.

Results.
A total of 130 patients were sedated, and the DS-DAT was completed in 106 patients at least once. The median duration of the sedation in these 106 patients was 25.5 hours (range 2-161). The mean score of the DS-DAT in the phase before sedation was 12.16 (95% CI 9.83-14.50) and decreased significantly to 8.06 (95% CI 5.53-10.58) in the titration phase of sedation. The mean score of the DS-DAT in the final phase of sedation was 7.42 (95% CI 4.90-9.94).

Conclusion.
This study shows that CPS is associated with a decrease in the level of discomfort within an acceptable time frame, although in some sedated patients higher levels of discomfort in the last hours of life occurred. Although the DS-DAT seems to be of value for monitoring the level of discomfort during CPS, the results of this study should be interpreted within the constraints of the limitations, and further research on the psychometric properties of this tool is needed before the DSDAT can be used in clinical practice.

Chapter 6

INTRODUCTION

When all options to treat severe burdensome symptoms in terminally ill patients have been exhausted or treatments are associated with unacceptable side effects, the use of palliative sedation (PS) can be considered.[1-4] PS is the intentional lowering of consciousness of a patient in the last phase of life.[1] The objective of PS is to alleviate discomfort caused by refractory symptoms.[1-4] The gold standard for detecting distress is patient self-report.[5] However, patients who are sedated cannot be consulted as PS produces an impaired capacity to communicate, which places them at a higher risk of unrelieved discomfort.[3,4,6] Therefore, we have to rely on subjective assessments of professionals or on observer rating scales in sedated patients. Such assessments focus on signs of discomfort rather than signs of comfort, and, therefore, a decrease of discomfort can be interpreted as an increase of comfort.

Although there is no evidence that monitoring PS with observer scales results in better symptom control, it seems plausible that the use of an observational assessment instrument helps to ensure that the patient becomes comfortable while sedated, prevents unnecessary dose escalation, and improves communication between professionals and the patients' families.[7,8] Several authors emphasize the need for clinical research on the efficacy in terms of a patient's comfort and control of refractory symptoms during palliative sedation.[8-12] However, a review of PS guidelines shows that only five of nine guidelines recommend specific assessment methods to monitor palliative sedation, and these are mostly focused on the level of consciousness rather than on discomfort.[9] One of the scales recommended by the European Association for Palliative Care is the Richmond Agitation-Sedation Scale.[2] The Richmond Agitation-Sedation Scale is used to standardize the sedation level in response to sedatives and hypnotics and is a numerical scale ranging from +4 to -5 (+4 for combative state and -5 for unarousable state with no response to voice or physical stimuli).[13] Only a score of -5 on this scale corresponds with absent awareness and a state in which a patient shows no signs of discomfort, presuming that the patient does not experience suffering. However, palliative sedation should be applied proportionately; that is, for consciousness to be lowered to the extent that is necessary and sufficient to relieve symptoms to the degree desired.[1,3,4] Only under exceptional circumstances is immediate titration to an unarousable state with no response to voice or physical stimuli required, for example, in case of terminal restlessness or in a catastrophic event such as massive bleeding or asphyxia caused by airway obstruction. Therefore, the aim of monitoring the level of consciousness with this scale is not to score discomfort but to alert the physician if the sedation is too deep. The Critical-Care Pain Observation Tool, another scale recommended by the European Association for Palliative Care to help assess pain and distress in patients with a lowered consciousness, was developed to monitor a specific symptom instead of discomfort in patients admitted to an intensive care unit, and requires the application of physical stimuli.[2] Furthermore, according to a systematic review, only a minority of patient-based studies on palliative sedation reported the use of observational scales, and most of these scales were used to monitor only the depth of sedation and not the quality.[8] The few scales used in these studies to monitor on a symptom level were based on the evaluation by the attending nurse or physician using a Likert or visual analog scale. Therefore, little is known about the course of discomfort in sedated patients, the efficacy of PS, and the determinants of discomfort during PS. For the latter, such determinants could help physicians identify patients who are at risk of higher levels of

discomfort during sedation. In these patients, intensive monitoring and evaluation of the administration of continuous palliative sedation (CPS) could help to achieve more comfort in sedated patients, especially in the last hours of their lives. To the best of our knowledge, only the prospective study of Morita and colleagues reported on this topic and found no significant differences in patient age, sex, performance status, icterus, target symptoms for sedation, and sedative medications between the patients with adequate and inadequate symptom relief.[14]

In the absence of a gold standard or a validated scale, the Discomfort Scale-Dementia of Alzheimer Type (DS-DAT) may be a good observer scale for monitoring the level of discomfort in sedated patients. The DS-DAT was developed for determining discomfort in patients with advanced dementia of Alzheimer type.[15] These patients have lost their cognitive capacity and verbal communication ability and are dependent on nursing staff to assess and treat their discomfort, which is similar to patients undergoing PS. In addition, the face validity of this scale for monitoring discomfort in sedated patients appears to be good, as the items of the scale correspond to the current clinical assessment and the recommendations of some guidelines of measuring discomfort by facial expressions and body movements.[3,16] Moreover, the DSDAT focuses on discomfort instead of individual symptoms like other instruments used in research on PS, appears to be more objective compared to Likert scales, does not require applying (pain) stimuli, and can be carried out by physicians as well as nurses.[7,8] The main objective of this study was to identify the course of discomfort using the DS-DAT in patients receiving CPS, who were admitted to a hospice or nursing home-based palliative care unit (PCU). A secondary goal of this study was to identify patient-related determinants of discomfort in last hours of life of sedated patients.

Methods

Setting, Patient Population, Data Collection, Follow-Up, and Inclusion Criteria

This study involved a prospective observational multicenter study performed between March 2011 and December 2012 in six hospices and three nursing home PCUs in The Netherlands with a follow-up period of three months. Patient admission to these settings was based on an estimated life expectancy of less than three months according to the referring physician. In case of a new admission during the study period, the attending physician invited the patient or their representative (in cases of a decision-incompetent patient) to participate via oral and written communication. The data collection ended when the patient died, was discharged, or at the end of the follow-up period. For analysis, inclusion criteria were written informed consent and the use of CPS.

Measures/Assessments

The attending physician recorded the patient's diagnosis using a tick box based on the International Classification of Diseases and Related Health Problems 10th Edition.[17] As soon as an indication for CPS occurred according to the attending team, the physician recorded: patient's intake the day before the start of CPS (no intake; only sips of fluid and no food; small amounts of fluid [less than 1 L] and none or minimal amount of food; normal fluid intake [more than 1 L] and skips meals; normal fluid and food intake), the refractory symptom for CPS (pain, dyspnea, delirium [according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised], vomiting, nausea, anxiety, exhaustion, existential suffering, and other [more than one answer possible]), whether they withheld, withdrew, started, or continued

artificial hydration, and the date and time of the start and end of CPS.[18] After the patient died, the effect of CPS on symptom relief according to the physician was recorded (four-point scale: no, hardly, partially, completely).

CPS was defined as "PS administered until death." This definition excluded situations in which medication was administered in normal doses to relieve insomnia and/or anxiety, where sedation was an unintended side effect of medication or where PS was only administered temporarily. During a half-day training session for the participating physicians, the definitions in the study protocol were explained to the physicians, and patient cases were used to clarify the criteria for CPS. Because of the observational study design, the protocol did not formulate under what conditions the decision-making process should take place, and the attending physician determined the indication for CPS.

To prevent bias, independent monitoring of the level of discomfort was carried out by nurses not involved in the daily care of the patient. The independent nurse was informed by the attending team immediately when sedation was indicated. The DS-DAT was assessed by the independent nurses just before the start of CPS and twice daily thereafter. The DS-DAT is a relatively complex scale, especially scoring of intensity, duration, and the number of items.[19] Therefore, before the start of the study, all independent nurses (n = 58) were instructed and practiced how to use the scale during a training session, in which an instructional Digital Versatile Disc was shown. They also were instructed not to share information with and receive

Item
A. Noisy breathing Negative sounding noise on inspiration or expiration; breathing looks strenuous, labored, or wearing; respirations sound loud, harsh, or gasping; difficulty breathing or trying hard at attempting to achieve a good gas exchange; episodic bursts or rapid breaths or hyperventilation.
B. Negative vocalization Noise or speech with a negative or disapproving quality; hushed low sounds such as constant muttering with guttural tone; monotone, subdued, or varying pitched noise with a definite unpleasant sound, faster rate than a conversation or drawn out as in moan or groan; repeating the same words with a mournful tone; expressing hurt or pain.
C. Content facial expression Pleasant calm looking face; tranquil, at ease, or serene; relaxed facial expression with a slack unclenched jaw; overall look is one of peace.
D. Sad facial expression Troubled looking face; looking hurt, worried, lost, or lonesome; distressed appearance; sunken, "hang dog" look with lackluster eyes; tears; crying.
E. Frightened facial expression Scared, concerned looking face; looking bothered, fearful, or troubled; alarmed appearance with open eyes and pleading face.
F. Frown Face looks strained; stern or scowling looks; displeased expression with a wrinkled brow and creases in the forehead; corners of mouth turned down.
G. Relaxed body language Easy openhanded position; look of being in a restful position and may be cuddled up or stretched out; muscles look of normal firmness and joints are without stress; look of idle, lazy of "laid back"; appearance of "just killing the day"; casual.
H. Tense body language Extremities show tension; wringing hands, clenched fist, or knees pulled up tightly; look of being in a strained and inflexible position.
I. Fidgeting Restless impatient motion; acts squirming of jittery; appearance of trying to get away from hurt area; forceful touching, tugging, or rubbing of body parts.

Fig. 1. Discomfort Scale—Dementia of Alzheimer Type (DS-DAT) items. Adapted from Hurley AC, Volicer BJ, Hanrahan PA, Houde S, Volicer L. Assessment of discomfort in advanced Alzheimer patients. Res Nurs Health 1992; 15:369—377.

information from the clinical staff during the study to prevent contamination. The DS-DAT consists of nine four-point items, and the summed scores range from 0 (no observed discomfort) to a maximum of 27 (high level of observed discomfort). The items are noisy breathing, negative vocalization, sad facial expression, frightened facial expression, frown, tense body language, fidgeting, content facial expression, and relaxed body language (Fig. 1). Scores are based on frequency, intensity, and duration of the observed behavior over five minutes and range from 0 (not observed) to 3 (present in high intensity and for almost the entire rating period). To calculate the summed scores, the scores of the two "positive items" (content facial expression and relaxed body language) are reversed. Discomfort is defined by the developers of the scale as a negative emotional and/or physical state, subject to variation in magnitude in response to internal or environmental conditions.[15] The validity and reliability of the (Dutch translation of the) DS-DAT have been shown in several studies in Alzheimer patients, with reliability and validity coefficient alpha scores ranging from 0.67 to 0.98.[15,20-24]

Ethical Considerations

The study followed the guidelines for good clinical practice and was conducted after approval of the research ethics committee of the Radboud University Medical Centre (ref 2010/407). For patients who did not participate in this study, only anonymous demographic data were collected.

Statistical Analysis

All patients with at least one DS-DAT assessment were included in the analysis. We grouped the assessments of the DS-DAT into four time frames: "phase before sedation," "titration phase of sedation," "in between phase," and "final phase of sedation." For the time frame "phase before sedation," all assessments until 15 minutes after the start of CPS were included. For the time frame "titration phase of sedation," all assessments between 15 minutes and eight hours after the start of CPS were included. The time frame "final phase of sedation" is referring to assessments performed in the period between eight hours preceding death and the moment of death. The remaining assessments were included in the "in between phase."

A mixed model was used to analyze the repeated assessments of the DS-DAT and to calculate the mean group score of the DS-DAT for the different time frames, with 95% CIs. The group means were controlled for the following covariates: age; gender; the diagnosis of malignant neoplasms; chronic lower respiratory diseases; and symptoms of pain, dyspnea, delirium, anxiety, exhaustion, and existential distress. Assessments of DS-DAT were excluded when the "titration phase of sedation" and the "final phase of sedation" coincided. This overlap in time frames could occur in case of a short survival after the administration of CPS.

For analyzing the association between patients' characteristics and the level of discomfort close to death, the assessments of the DS-DAT in the "final phase of sedation" were used. If multiple assessments per patient were present in this phase, the assessment closest to the moment of death was used.

Descriptive analysis was performed using proportions for categorical variables and means ± standard deviations for continuous variables. For analyzing the association between patients' characteristics, recorded by the attending team, and the level of discomfort as dependent continuous variable, recorded by the independent nurse, Student t-test was used for dichotomous independent variables, analysis of variance for categorical independent variables and the Pearson correlation for continuous independent variables. For analyzing the differences in the mean scores of the DS-DAT for the different time frames, a

t-test was used. All P-values were two-sided, and an alpha of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (IBM/SPSS, Inc., Armonk, NY).

Results

During the study period, 503 of 803 admitted patients (62.6%) gave written informed consent. Patients with written informed consent did not differ from those without with regard to gender (P = 0.20), age (P = 0.12), and diagnosis. A total of 467 patients died; 130 of these patients (27.8%) received CPS (Fig. 2). Most of the sedated patients were women of advanced age, and the majority of the patients had cancer (Table 1). For 106 sedated patients, the DS-DAT was completed at least one time, with a median of three and a range of 1-14 assessments per patient, resulting in a total of 352 DS-DAT assessments across all phases. The median duration of the sedation was 25.5 hours (range 2-161), with a mean duration of 34.2 hours (SD 31.4). In 97.1% of cases, the physician withheld artificial hydration during CPS, and in 2.9% of cases, the physician continued artificial hydration (data not shown).

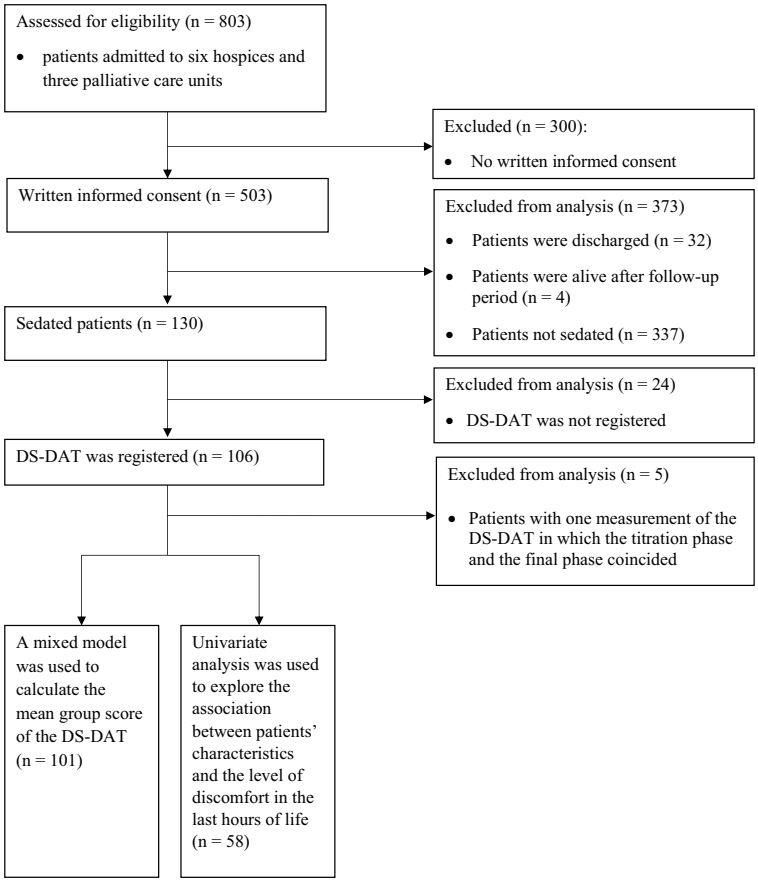

Fig. 2. Flowchart of patients throughout the study. DS-DAT = Discomfort Scale–Dementia of Alzheimer Type.

Mean Score of Discomfort in Different Time Frames

For 16 assessments of the DS-DAT, "the titration phase" and "the final phase" coincided, resulting in a sample of 101 patients with a total of 336 DS-DAT assessments. The adjusted mean score of the DS-DAT in the phase before sedation was 12.16 (95% CI 9.83-14.50), and this decreased significantly to 8.06 (95% CI 5.53-10.58) in the titration phase of sedation and remained relatively stable until the moment of death (Table 2). A significant reduction in discomfort compared to the phase before sedation was found for all three of the following phases of CPS ($P < 0.001$).

Association Between Patients' Characteristics and the Level of Discomfort Close to Death

A total of 58 patients fulfilled the study criteria for the analysis between patients' characteristics and the level of discomfort in the final phase of sedation (Fig. 2). The median time between the assessment of the DS-DAT in the final phase of sedation and the moment of death was 251 minutes (SD 125). The mean duration of CPS in these patients was 36.86 hours (SD 30.17), with no significant association between duration of CPS and the level of discomfort in the last eight hours of life ($P = 0.427$, data not shown). Gender, age, and the presence of malignant neoplasms were not significantly associated with the level of discomfort during sedation in the last eight hours of life ($P = 0.911$, $P = 0.299$, $P = 0.737$, respectively, data not shown). Patient intake of a small amount of fluid and none/minimal amount of food or more the day before the start of sedation ($P = 0.045$), the presence of the refractory symptom vomiting ($P = 0.014$), and the presence of multiple refractory symptoms ($P = 0.049$) were positively associated with a higher mean discomfort score during the last eight hours of life (Table 3).

In cases in which, according to the physician's opinion, CPS provided complete symptom relief (n = 46), the mean score of the DS-DAT was 4.61 (SD 3.41). In cases in which, according to the physician's opinion, CPS provided no to partial symptom relief (n = 11), the mean score of the DS-DAT was significantly higher (7.09 [SD 3.56]; $P = 0.026$, data not shown).

Table 1
Demographic Characteristics of Sedated Patients (*n* = 130)

Characteristic	*n* (%)
Gender	
Male	61 (46.9)
Female	69 (53.1)
Age[a]	
<55 yrs	12 (9.2)
55–75 yrs	57 (43.8)
>75 yrs	61 (46.9)
Diagnosis[b]	
Malignant neoplasms	116 (89.2)
Heart failure	12 (9.2)
Dementia	3 (2.3)
Chronic lower respiratory diseases	10 (7.7)
Cerebrovascular diseases	3 (2.3)
Parkinson disease	1 (0.8)
Diabetes mellitus	3 (2.3)
Other diagnoses	12 (9.2)

[a]Mean age of 73.27 (SD 12.51).
[b]More than one diagnosis possible.

Table 2
Mixed Model: Mean Score of the Discomfort Scale—Dementia of Alzheimer Type (DS-DAT) in the Different Time Frames

Phase	Mean Score DS-DAT	95% CI
Phase before sedation	12.16	9.83–14.50
Titration phase of sedation	8.06	5.53–10.58
In between phase	7.82	5.48–10.16
Final phase of sedation	7.42	4.90–9.94

The group means were controlled in the mixed model for the following covariates: age; gender; the diagnosis of malignant neoplasms; chronic lower respiratory diseases; and symptoms of pain, dyspnea, delirium, anxiety, exhaustion, and existential distress. Age was evaluated at the following value: 71.70.
In "the phase before sedation," 79 DS-DAT assessments were performed, 48 DS-DAT assessments were performed in "the titration phase," 163 DS-DAT assessments were performed in "the in between phase," and 46 assessments in "the final phase." For 16 assessments of the DS-DAT, "the titration phase" and "the final phase" coincided.

Table 3
Association Between Patients' Characteristics and Discomfort Scale—Dementia of Alzheimer Type (DS-DAT) Score During the Final Phase of Sedation

Variable	*N* (%)	Mean Score (SD) DS-DAT	*P*-Value
Patient's intake the day before the start of CPS[a]			
Small amount of fluid and none/minimal amount of food or more	14 (24.1)	6.64 (3.32)	**0.045**
Only sips of fluid and no food or less	44 (75.9)	4.61 (3.20)	
Refractory symptom[b]			
Pain present	24 (41.4)	5.42 (3.11)	0.55
Pain not present	34 (58.6)	4.88 (3.49)	
Dyspnea present	20 (34.5)	5.10 (2.72)	1.00
Dyspnea not present	38 (65.5)	5.11 (3.62)	
Delirium present	16 (27.6)	6.44 (4.07)	0.11
Delirium not present	42 (72.4)	4.60 (2.88)	
Vomiting present	4 (6.9)	9.00 (3.65)	**0.014**
Vomiting not present	54 (93.1)	4.81 (3.14)	
Nausea present	6 (10.3)	4.83 (2.64)	0.84
Nausea not present	52 (89.7)	5.13 (3.41)	
Anxiety present	14 (24.1)	6.00 (3.70)	0.25
Anxiety not present	44 (75.9)	4.82 (3.18)	
Exhaustion present	33 (56.9)	5.24 (3.43)	0.72
Exhaustion not present	25 (43.1)	4.92 (3.23)	
Existential suffering present	14 (24.1)	5.43 (3.59)	0.68
Existential suffering not present	44 (75.9)	5.00 (3.26)	
Other symptom present	11 (19.0)	5.55 (4.16)	0.63
Other symptom not present	47 (81.0)	5.00 (3.13)	
Number of refractory symptoms			
1	15 (25.9)	4.13 (3.14)	**0.049**[c]
2	17 (29.3)	4.18 (2.63)	
3	14 (24.1)	6.29 (3.75)	
4	9 (15.5)	5.44 (2.74)	
5	3 (5.2)	8.67 (4.93)	

CPS = continuous palliative sedation; ANOVA = analysis of variance.
Values in bold are significant.
In 54 patients, one assessment of the level of comfort was taken by the independent nurse during the last eight hours, and in four patients, there were two observations.
[a]Category "normal fluid and food intake": 0 patients, category "normal fluid intake and skips meals": 1 patient, category "small amount of fluid and none or minimal amount of food": 13 patients, "only sips of fluid and no food": 35 patients, and category "no intake": 9 patients.
[b]More than one indicating symptom for CPS possible.
[c]ANOVA for factors with ordered levels.

Discussion

To the best of our knowledge, this is the first study to prospectively investigate the level of discomfort before and during the administration of CPS measured independently by the DS-DAT. This study showed that discomfort significantly decreases within eight hours after the start of CPS and remains relatively stable until the moment of death. Furthermore, this study showed that an intake of at least a small amount of fluid before sedation, the presence of the refractory symptom vomiting and the presence of multiple refractory symptoms were positively associated with a higher mean score of the DS-DAT during the last eight hours of life.

Results in Relation to Other Studies and Potential Mechanisms

Although CPS is increasingly considered to be an ethically and legally acceptable therapy for a select group of patients,[1-4] evidence regarding the efficacy of this intervention is scarce. This study showed that the administration of CPS appears to be an effective intervention for treating refractory symptoms. Moreover, even in the first eight hours after the start of CPS during which the physician has to titrate the medication, the level of discomfort decreased significantly and remained at a median score of lower than eight. Although there is no cutoff point of the DS-DAT that reflects comfort in patients with CPS, a score of eight is mentioned in the literature as the cutoff point for high vs. not high discomfort in a population of confused elderly patients or patients with dementia.[21,22] In our opinion, the DS-DAT is potentially a useful scale for measuring comfort during CPS in combination with the subjective assessment of the physician and the nurse. Our finding that CPS provided complete symptom relief according to the physician was associated with a lower mean score of the independently measured DS-DAT seems to support this.

Regarding the association with a higher mean score of the DS-DAT in the last hours of life, the presence of a higher intake before the administration of CPS may result in additional discomfort, which could be due to an increase of ascites, peritumor and pulmonary edema, or salivary and gastrointestinal secretions with more associated symptoms.[4,25] Our finding that vomiting and multiple symptoms were associated with higher levels of discomfort warrants further explanation. It is possible that vomiting will not be diminished under sedation and new discomfort due to aspiration is induced, both resulting in a higher level of discomfort. For multiple symptoms, the potential mechanism is unclear. Although CPS aims to alleviate discomfort, apparently the presence of more refractory symptoms before the start of CPS makes it difficult to accomplish comfort during sedation. Existing symptoms may exacerbate other symptoms or may evolve into a cascade of symptoms, eventually leading to a greater increase of discomfort compared to solitary symptoms.

Strengths and Limitations

The strength of this study is the independent monitoring of the comfort of a highly vulnerable patient group: sedated patients. Monitoring of patients was performed in a carefully designed prospective multicenter study.

Nevertheless, some limitations warrant attention. The most important limitation of this study is the use of a tool that is validated for monitoring the level of discomfort in cognitively impaired (dementia) patients and not in continuously sedated patients. Research on measuring discomfort in Alzheimer patients has found that the DS-DAT has good psychometric properties. However, its validity and reliability has not been shown in sedated patients, and we did not test psychometric properties of the DS-DAT in this population before this study. Notwithstanding this, in our opinion, the DS-DAT has a good face validity. Most items seem valid for determining discomfort in sedated patients, except perhaps the item "noisy breathing." Here, it is possible that the observer scored this item of the DS-DAT in cases in which a "death rattle" was present, whereas it is doubtful whether sedated patients actually experience discomfort from this symptom.[26] Second, we categorized the assessments of the DS-DAT into different time frames, with a length of eight hours of the titration and final phases of sedation. Although this length of time is arbitrary, our assumption was that it is desirable to achieve comfort for the total duration of the administration of CPS and at least in the last hours of life. Focusing on these last hours of life, the attending physician was able to titrate the medication; therefore, comfort should have been achieved in most cases. In addition, for the time frame "phase before sedation," all assessments until 15 minutes after the start of CPS were included. This time frame was based on the Tmax of midazolam after subcutaneous injection, the drug of choice for inducing CPS,[1,27-31] which makes assessment of the maximum effect of midazolam only possible after 15 minutes. However, five assessments took place 15 minutes after the start of CPS, and we cannot rule out some effects on discomfort by the medication used to initiate CPS in these assessments. Third, in the different time frames of CPS, the patient population differed, partially due to variation in the duration of CPS in individual patients and partially due to an absence of the independent nurse in some cases. For the latter, a time delay between the decision for CPS and the arrival of the independent nurse occurred and, therefore, in some cases, the administration of CPS occurred before the assessment of the DS-DAT was possible. However, we addressed this limitation using a mixed model and correcting for multiple covariates. Fourth, the assessments of the DS-DAT during CPS took place only twice a day. We cannot rule out that scores of DS-DAT between the assessments of the independent nurse could differ then registered in our study, especially in case of the presence of delirium. Finally, this study was performed in hospices and nursing home PCUs in The Netherlands. The findings in this study may not be generalizable to other populations, care settings, and countries.

Conclusion

This study showed that the administration of CPS is associated with a decrease in the level of discomfort and appears to be an effective intervention for refractory symptoms in the final days of a patient's life. Furthermore, physicians should be aware that higher levels of discomfort in the last eight hours of life could be present in sedated patients who have an intake of a small amount of fluid of more before CPS, who have the refractory symptom vomiting and who have multiple refractory symptoms. The DS-DAT, an observer-based rating scale, is potentially a useful scale for measuring discomfort during CPS in combination with the subjective assessment of the physician and the nurse. However, the results of this study should be interpreted within the constraints of the given limitations, and before the DS-DAT can be used in clinical practice, further research on the reliability and validity of the DS-DAT is recommended. Such research should focus on the (face) validity of this tool, for example, using the Delphi method, and on its interrater and intrarater reliability. In addition, to obtain some concurrent validity, comparison between simultaneously assessments of the DS-DAT and subjective assessments of physicians and nurses should be performed.

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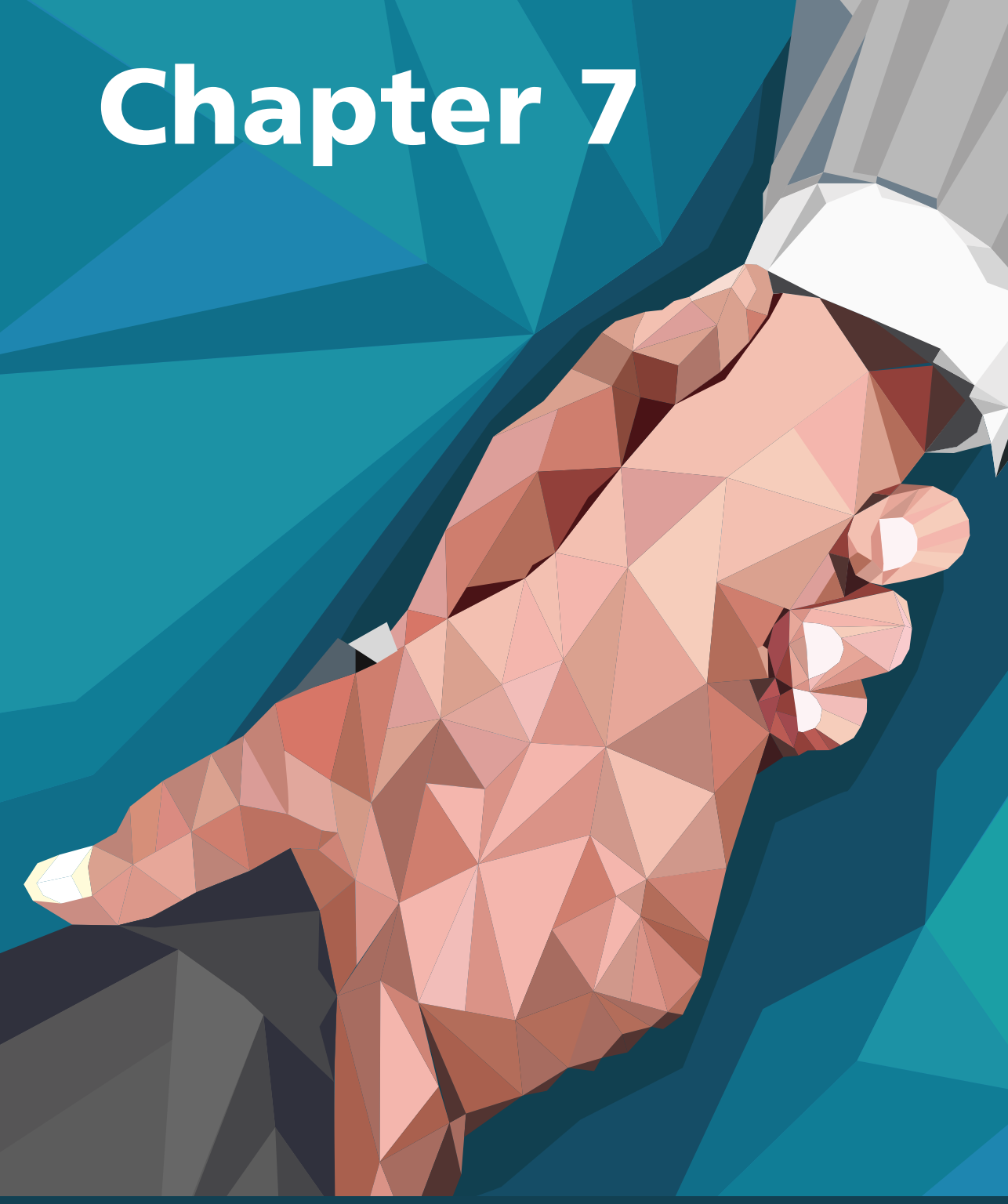
Chapter 7



General discussion

Chapter 7

General discussion

Introduction

Palliative sedation involves the deliberate lowering of a patient's level of consciousness in the last stages of life. Palliative sedation can be administered if one or more symptoms (so-called refractory symptoms) in a dying patient causes unbearable suffering and conventional modes of treatment are not effective or fast-acting enough and/or if these modes of treatment are accompanied by unacceptable side-effects.[1-4] Palliative sedation refers to brief, intermittent or continuous palliative sedation (CPS).[1] CPS must be considered as a last resort intervention. CPS not only takes away a patient's suffering until the moment of death but also produces an impaired capacity to communicate, which takes away potential positive and meaningful experiences a patient might have.[4-10] In addition, relatives, nurses and physicians sometimes experience the administration of CPS as a burden.[11-17]

The introduction of the Dutch national guideline on palliative sedation in 2005 gave a comprehensive framework for clinical decision-making. Moreover, there has been a remarkable increase in the number of empirical studies involving palliative sedation since 2000. However, there are still unanswered questions regarding the administration of CPS.[1,18] Especially little is known about the determinants of the administration of CPS in general, the practice of CPS as performed by elderly care physicians and the outcome of this intervention in their patients. The main goal of the research described in this thesis was to provide more insight into these specific topics. In this final chapter, the main results of the studies presented in this thesis will be summarized. Also the methodological considerations and implications for clinical practice, health care policy and future research are provided.

Summary of findings

To answer the research questions formulated in the introduction of this thesis, we performed a systematic review of the literature, and designed a structured questionnaire and a prospective observational multicenter study. The questionnaire was sent to registered members of the Dutch Association of Elderly Care Physicians and Social Geriatricians. The prospective study was performed in six hospices and three nursing home-based palliative care units in the Netherlands. A summary of answers found is given below.

Which determinants of the administration of continuous palliative sedation are known in the published literature?

In our systematic review, nine factors were found to be associated with the administration of CPS (chapter 2). Eight factors showed an increased probability for the administration of CPS: patients who were younger; patients who were male; patients with a cancer diagnosis; patients with feelings of hopelessness; patients dying in a hospital; and patients whose attending physicians were very or extremely nonreligious, working in "other hospital" specialties, or in favor of assisted death. The factor "patients living in a Dutch-speaking community setting in Belgium" showed a decrease in the probability of receiving CPS.

Are age, gender, diagnosis, use of opioids or psycholeptics, number of medications, functional status, symptom distress and level of consciousness at the time of admission to a hospice or nursing home-based palliative care unit associated with the administration of continuous palliative sedation at the end of life?

The results of our prospective study showed that only the use of opioids at admission was significantly independently associated with the administration of CPS (chapter 3). For the use of psycholeptics a marginally significant independent association was found. Although we focused on patient-related factors, this study showed also that residence was associated with the administration of CPS.

What is the practice of continuous palliative sedation by Dutch elderly care physicians?

The respondents of our questionnaire described 316 cases of sedated patients (chapter 4). The majority of the patients were aged, women and had cancer or dementia. In all but one case, informed consent for the administration of CPS was obtained from the patient or the relative who was the patient's legal representative. Eighty-two percent of patients were treated with CPS for two or more refractory symptoms, mostly pain, anxiety, exhaustion, dyspnea, delirium, loss of dignity, and existential distress. If there was only one refractory symptom, it was usually dyspnea, pain, or exhaustion. In 98% of cases, CPS was aimed at symptom relief. Of patients with cancer, 17% had previously requested euthanasia. Life expectancy and the duration of CPS were 7 days or less in almost all patients. According to the respondents, CPS provided complete symptom relief in 89% of the cases. More than half of the patients were unresponsive to physical stimuli at the time adequate symptom relief was attained and must be qualified as being under deep and continuous sedation. For 82% of patients, intake was less than 500 mL before the start of CPS, and in most cases artificial hydration was withheld during CPS. Midazolam was the most frequently used drug to facilitate the start and continuation of CPS. The mean starting dose of midazolam was 31 mg every 24 hours (range 0–240 mg/24 h), and the mean end dose was 48 mg every 24 hours (range 0–480 mg/24 h). Twenty-six percent of all physicians estimated that the use of CPS had shortened patients' life span.

Do Dutch elderly care physicians fulfil the preconditions for administering continuous palliative sedation in cases in which existential suffering is present?

The results of our questionnaire showed that other refractory symptoms were also reported by elderly care physicians for most of the patients with refractory existential suffering and that life expectancy was seven days or less (chapter 5). Furthermore, informed consent for initiating CPS had been obtained in all cases. However, consultation and intermittent sedation before the start of CPS were far less frequently reported than one would expect based on the preconditions mentioned in guidelines and recommendations.

What is the course of discomfort in patients admitted to a hospice or nursing home-based palliative care unit receiving continuous palliative sedation?

In our prospective study, the Discomfort Scale–Dementia of Alzheimer Type (DS-DAT) was independently assessed for monitoring patient discomfort just before and during CPS (chapter 6). The results showed that discomfort, measured by the DS-DAT, significantly decreases within 8 hours after the start of CPS and remains relatively stable until the moment of death.

Which characteristics of patients admitted to a hospice or nursing home-based palliative care unit determine (dis)comfort during the administration of continuous palliative sedation?
The results of our prospective study showed that the patient's intake of a small amount of fluid or more just before CPS, the presence of vomiting or multiple symptoms were positively associated with a higher mean score on the DS-DAT during the last eight hours of life. Gender, age and the presence of malignant neoplasms and the refractory symptoms pain, dyspnea, delirium, nausea, anxiety, exhaustion, existential suffering and other symptoms were not significantly associated with the level of discomfort close to death during sedation (chapter 6).

Methodological considerations

The articles presented in this thesis focused on relatively unexplored topics related to the administration of CPS. The strengths of the studies in this thesis were a nationwide retrospective and a multicenter prospective design, the use of clear definitions of CPS and refractory symptom, and a large study population. Despite these strengths, the presented studies also had some important methodological considerations and limitations that should be taken into account when interpreting the results.

This thesis concerns the administration of CPS in general. Most patient-based studies performed over the past 15 years have focused on continuous deep sedation, which is a subtype of CPS.[12,19-38] Therefore, care should be taken when comparing the results of the patient-based studies presented in this thesis with the results of previous international studies. In the Netherlands, there are two approaches to the depth of continuous sedation among physicians: starting with mild sedation and only increasing the depth if necessary, and deep sedation right from the start.[39] The approach of deep sedation right from the start put the focus on the depth of the sedation instead of the presence or absence of discomfort. By taken this approach, waking during CPS is considered to be problematic, even in cases in which the patient is comfortable. In such cases, patient relatives could exert pressure on the physician for rapid dose escalation, creating more problems if the dose escalation does not have the desired effect. The Dutch national guideline and other guidelines on palliative sedation advise physicians to titrate sedatives, which means that the dose of sedative is adjusted to the level needed for proper relief of symptoms, and consciousness is reduced no more than necessary to adequately relieve suffering.[1-3] A result of this recommendation is that immediate titration to an unarousable state with no response to voice or physical stimuli is required only under exceptional circumstances, e.g., in cases of terminal restlessness or in a catastrophic event such as massive bleeding or asphyxia caused by airway obstruction. Furthermore, patient-based research shows that deep sedation, i.e., no response to physical stimuli, is not always required.[26,40-42]

In the retrospective and prospective study, clear definitions of palliative sedation, CPS and refractory symptom were used, and these definitions were in agreement with the Dutch national guideline on palliative sedation.[1] However, specific items such as existential suffering and exhaustion were not properly defined. In the palliative care community, there is still a lack of consensus on a definition of existential suffering. Conceptions of existential suffering at the end of life may include (individually or in combination): loss of a sense of personal meaning; loss of a sense of life's purpose; fear of death; feelings of despair, anguish, and hopelessness; perception of being a burden to others; sense of betrayal; sense of helplessness; and loss of dignity.[43] In chapter 5, patients with existential suffering were defined as those patients for whom the respondent had filled in the tick box for existential suffering and/or loss of dignity

as a refractory symptom. However, we did not include exhaustion. Exhaustion can be caused not only by the physical deterioration due to terminal disease but also by the complex social interactions between patients and relatives, the struggle with loss of control, as well as by fear of the future.[44] The lack of a clear definition of existential suffering in the retrospective study has given rise to the risk of physicians making inconsistent diagnoses; this inconsistency could have biased the validity of our results. It would be worthwhile to develop a consistent definition of existential suffering for the palliative care community because the lack of consensus on such a definition further hinders discussion and research efforts.

One of the objectives of this thesis was to observe the course of discomfort in patients receiving CPS. The gold standard for detecting distress is patient self-reporting.[45] However, most patients who are sedated cannot be consulted as CPS produces an impaired capacity to communicate.[3,4,7] Therefore, we have to rely on subjective assessments by professionals or on observer-based rating scales in sedated patients. Currently, there is no validated and generally accepted scale for monitoring discomfort in sedated patients. Due to the absence of a gold standard to monitor discomfort (and comfort) in sedated patients, validation of such a scale seems to be hard and raises several limitations. These limitations hamper the development of a scale that can be used in research and clinical practice. In the prospective study of this thesis, discomfort before and during the administration of CPS was assessed using the DS-DAT. In our opinion, the DS-DAT may be a good observer-based scale for monitoring the level of discomfort in sedated patients. Unfortunately, this scale is not yet validated for sedated patients and we did not perform such a study either. Nevertheless, there are arguments to explain our choice of this scale. The DS-DAT was developed for determining discomfort in patients with advanced Alzheimer type dementia,[46] and several studies in Alzheimer patients have shown that the DS-DAT has good psychometric properties.[46-51] Patients with advanced dementia have lost their cognitive capacity and verbal communication ability and are dependent on nursing staff to assess their discomfort, which is similar to patients undergoing CPS. Additionally, the face validity of this scale for monitoring discomfort in sedated patients appears to be good. The items of the scale correspond to the current clinical assessment and the recommendations of some guidelines for measuring discomfort by facial expressions and body movements.[3,52] Moreover, the DS-DAT focuses on discomfort instead of individual symptoms such as other instruments used in research on PS or as recommended by guidelines (e.g., the Critical Care Pain Observation Tool).[2] Additionally, the DS-DAT appears to be more objective compared with Likert scales, does not require applying (painful) stimuli, and can be carried out by physicians as well as nurses.[53,54] Furthermore, the DS-DAT includes not only items related to discomfort but also items related to comfort (i.e., relaxed body language and content facial expression). In addition, the prospective study showed an association between the administration of CPS and a decrease in the level of discomfort afterward. Such an association demonstrates at least some content validity. Furthermore, the finding that CPS provided complete symptom relief according to the physician was associated with a lower mean score on the independently measured DS-DAT close to death indicates some concurrent validity, despite the fact that the assessments were not performed simultaneously.

To prevent bias in the observational prospective study, i.e., to prevent changes in clinical management based on the outcome of the DS-DAT, independent monitoring of the level of discomfort was carried out by nurses not involved in the daily care of the patient. To limit the workload and make scheduling easier, these assessments were only scheduled just before the start of CPS and twice daily during the daytime

thereafter with fixed time windows. However, this design caused some (methodological) implications. First, we acknowledge that this design does not reflect clinical practice, and we cannot rule out that the discomfort of a patient in between the assessments by the independent nurse could differ from their observed DS-DAT scores, especially in case of the presence of delirium. Second, due to logistic problems related to the involvement of independent nurses, in some patients (some of) the assessments could not be performed. Third, the fixed time windows of the assessments caused differences in the time interval between the start of CPS and the first assessment using the DS-DAT after the start between patients. Due to missing data and differences in the time interval between the assessments, we could not compare the individual course of discomfort between patients receiving CPS. In order to calculate the mean group score of the DS-DAT, we categorized the assessments of the DS-DAT into different timeframes, with a length of eight hours for the titration and the final phase of sedation. Although this length of time was arbitrary, our assumption was that it is desirable to achieve comfort for the total duration of the administration of CPS and specially in the last hours of life. Focusing on these last hours of life, the attending physician was able to titrate the medication, and therefore comfort should have been achieved in most cases. In these different timeframes of CPS, the patient population differed, partially due to variation in the total duration of CPS in individual patients and partially due missing assessments. We addressed this difference using a mixed model and correcting for multiple covariates.

In the prospective study a number of protocol violations of the assessment of the Edmonton Symptom Assessment System (ESAS), missing ESAS and missing components of some patients' ESAS were present. All could influenced the power of the study and therefore its validity. Therefore, multivariate models with and without multiple imputation were used to control for understating uncertainty. These models showed a similar association. In studies in which research is combined with the daily care of patients, especially in a population of frail and highly vulnerable patients, protocol violations and missing data can be present. All residences were regularly visited during the study period to collect the data and to monitor the execution of the research protocol. During these visitations, nurses were asked for the reasons regarding the protocol violations and missing data. They often mentioned not only the work load with the daily care of patients as a reason but also the fear of burdening the patient, who already might be experiencing distress because of the admission and the presence of (non)physical symptoms. We did not ask the patients the reasons why they decided whether to take part in the study, but based on the information gathered from the physicians and nurses during the visitations, similar reasons were often present for patients who did not participate in the study. It seems that patients, although in a critical phase in life, are mostly willing to contribute to research. However, physicians and nurses have some reservations regarding burdening frail and vulnerable patients, and combining daily care and research is sometimes hard.

The response rate to the questionnaire was 54%, and 63% of the patients participated in the prospective study. The respondents to the questionnaire were representative of the total population of registered elderly care physicians with respect to sex and age, and the participating patients in the prospective study were a representative sample of the total population with respect to sex, age, KPS and diagnosis. However, selection and non-responder bias cannot be excluded.

Finally, care should be taken when generalizing the results presented in this thesis. The designs of the studies in the literature review varied with respect to population, setting, country, and attending physician. The results of the retrospective and prospective studies presented in this thesis focused on CPS administered by elderly care physicians. The Netherlands is the only country where elderly care physicians exist as an independent medical specialty with its own specialist training program.[55] Furthermore, the prospective study presented in this thesis was performed in hospices and nursing home palliative care units. Some of the results presented in this thesis seem to be applicable to the general practice of CPS regardless of country, setting or attending physician. However, cultural, legal, and organizational differences may exist that could potentially limit extrapolation.

Implications for clinical practice and health care policy

The results of the research described in this thesis give directions that are valuable for the care of patients in the palliative care trajectory and for optimizing the administration of CPS. These directions are discussed below, and summarized in table 1.

Monitor high-risk patients

Most of the reported determinants of the administration of CPS in this thesis were patient-related, e.g., patients who were younger, patients who were male, patients with a cancer diagnosis and patients who used opioids. From a clinical perspective, the use of opioids, the use of psycholeptics and patients with feelings of hopelessness are the most interesting of the patient-related determinants. These determinants can be acted upon early in the clinical palliative care trajectory. Appropriately applied interventions can alter the course of symptoms and thereby possibly limiting the patient's eventual future need for palliative sedation. For the use of opioids, it is not clear whether the association is a direct causal relationship due to side effects or an indirect relationship due to symptoms of dyspnea and pain. For the use of psycholeptics, we assume that this association could be a surrogate of an underlying delirium. The mechanism in patients with feelings of hopelessness is unclear; it could be a determining factor of the patient's endurance, and its presence may exacerbate suffering due to other symptoms. Although monitoring patients in the palliative care trajectory should be standard, in these high-risk patients extra screening for signs of opioid toxicity, the presence and intensity of delirium, pain, dyspnea and feelings of hopelessness should take place on a daily or at least weekly basis. Physicians and nurses must be competent in the assessment of the aforementioned symptoms, the correct treatment of such symptoms and the treatment of medication side effects prior to starting CPS. In the Netherlands, the Netherlands Comprehensive Cancer Organisation (IKNL) has established a national network of teams specialized in palliative care services that can be consulted to support and advise professional caregivers. Addiotionally, the attending physician can consult experts in the field of psychology or spirituality. If, despite such intensive assessments and consultations, symptoms evolve to a refractory state, palliative sedation should be considered.

Inform high-risk patients early in the palliative trajectory and motivate advance care planning

Advance care planning and information on the indication and preconditions for CPS early in the palliative trajectory are necessary in all high-risk patients, especially if two or more determinants are present. The importance of developing advance care plans in the palliative phase has been emphasized; however, many patients and their caregivers still do not discuss possible end-of-life scenarios in the final phases of life.[56] For patients who are sedated, more than half are not or only shortly before the start of CPS become involved in decision making.[26] In acute situations there is often insufficient time to make well-informed,

balanced decisions concerning CPS.[12] When patients and their relatives are suddenly confronted with discussions regarding CPS, death, loss of consciousness, and saying goodbye, high levels of stress can be experienced.[15,57,58] Especially in cases of a patient who is not competent to make decisions, relatives sometimes feel the burden of responsibility for the decision to use sedation.[58] Furthermore, the term palliative sedation is not well known among the general public in the Netherlands, and there is a variety of interpretations of the term.[59] These factors emphasize the importance of clearly informing patients and relatives about palliative sedation and of verifying their beliefs about and expectations of palliative sedation, because the beliefs and expectations of patient and relatives may differ from professional opinions and guidelines.[13] The moment at which advance care planning and the sharing of information on the indication and the preconditions for CPS in high-risk patients should take place can be debated. For high-risk patients admitted to a hospice or a PCU, such discussions could take place shortly after admission. Admission to these settings in the Netherlands is based on an estimated life expectancy of less than three months. At home or on admission to a hospital, the determination of the prognosis of a high-risk patient can be more challenging. The general practitioner or medical specialist could use the surprise question, i.e., would you be surprised if this patient died within the next three to six months?

Fulfil the preconditions for CPS for patients with existential suffering

Existential suffering is considered to be a condition that medical practitioners must address.[1,60] However, there is no general consensus on whether palliative sedation is an appropriate intervention for this type of suffering.[61] Existential suffering has different aspects from physical suffering. Existential suffering may occur long before the terminal phase, often tends to fluctuate, and psychological adaptation and coping are common.[2,62] Additionally, it can be difficult for practitioners to determine whether a patient's existential suffering is refractory, or to distinguish it from psychiatric conditions such as depression.[2,62,63] Although interventions for existential suffering are not well established and may not be suitable for all patients,[2,62-64] these findings may cause physicians to administer CPS in cases where other, more conventional therapies would be more appropriate. Furthermore, existential suffering such as demoralization and hopelessness is linked to terminally ill patients' desire for death.[65,66] Such a desire can result in a request for euthanasia, but should not be resolved by the administration of CPS. Despite the lack of a general consensus on whether palliative sedation is an appropriate intervention for existential suffering, the results presented in this thesis and in other studies show that existential suffering often proves to be a reason for administering CPS.[22,23,26,41,42,67] In these studies, existential suffering almost always coexists with refractory physical symptoms. Physicians suspect that the presence of certain physical symptoms is related to and may increase existential suffering and vice versa, accumulating into a 'refractory state'.[64,68,69] In addition, several guidelines and recommendations, including the Dutch national guideline on palliative sedation, identify existential suffering as a potential refractory symptom that can be treated with CPS under specific conditions (see table 1).[1-4,70-72] However, the results presented in this thesis show that the use of intermittent sedation and consultation with a palliative care consultant or spiritual counsellor before starting CPS were far less frequently reported than one would expect given the recommendations of the guidelines. These preconditions deserve more attention in clinical practice. Applying intermittent sedation before administering CPS would allow patients a time out and give healthcare providers a chance to reassess, possibly preventing a vicious cycle of existential suffering.[62] Although physicians are generally aware of the importance of recognizing and treating existential suffering at the end of life, this is not always included in advance care planning and training programs. Routine consultation with experts in the fields of psychology, psychiatry, or spirituality and religion is therefore recommended in such cases.[73]

Be aware of personal values in end-of-life care decision making

The prospective study on determinants in hospices and palliative care units in this thesis showed that residence is associated with the administration of CPS (chapter 3). Another study reported substantial clustering of the use of palliative sedation within physician practices.[74] In the review on determinants in this thesis, the place of death, i.e., the hospital, was found to be associated with the administration of CPS (chapter 2). Different standards of care, policies towards end-of-life interventions and complexity of clinical conditions in patients compared to other settings are mentioned as possible underlying factors for the umbrella term residence.

However, physician-related factors could also contribute to this type of clustering. The review showed that there was an increased probability of the administration of CPS in patients whose attending physicians were very or extremely nonreligious or were in favor of assisted death. Furthermore, the 'how' of determining the intolerability of suffering and refractoriness by physicians is not established in guidelines.[75] This omission can result in subjectivity in determining the refractoriness of symptoms and therefore to variation in the frequency of CPS.[2] Although this thesis could not identify the specific underlying factors of the umbrella term residence, physician and nursing staff should be aware that their own values may enter into the end-of-life care decision making.[76]

Inform patients and relatives of the effectiveness of CPS before starting and monitor patients during CPS

The results presented in this thesis showed that the administration of CPS is associated with a decrease in the level of discomfort within an acceptable timeframe. However, physicians and nurses should also be aware that higher levels of discomfort in the last eight hours of life could be present in some sedated patients. Therefore, physicians should not only communicate with patients and their relatives that CPS is in general a fast-acting and effective intervention, but also that CPS is not a one-size-fits-all intervention and that monitoring of patients' discomfort during sedation is essential. Currently, there is no validated and generally accepted scale for monitoring discomfort in sedated patients. Despite this absence, it is important to communicate prior to the start of CPS which signs of discomfort are looked for during sedation. Adequate communication regarding the roles and responsibilities of physicians, nurses and relatives during CPS is an essential part of that process.[77,78] Consequently, all actors are aware when drug dosage adjustments should be made. By explicitly communicating beforehand which signs of discomfort are monitored and when drug dosage adjustments are required, the fear of family members for possible suffering of their sedated beloved one will decrease.[12,15] For example, clear instructions on the clinical symptoms of Cheyne-Stokes respiration, death rattle and cyanosis can prevent different interpretations and increase the common sense of dying.[79] Adequate communication before the start of CPS on signs of discomfort and drug dosage adjustments may also prevent family members from becoming impatient or even considering it unacceptable for the dying process to take so long, in turn putting pressure on the doctor to speed up the dying process.[79] In clinical practice, the individual items of the DS-DAT, e.g., facial expression, body language, fidgeting and negative vocalization, can be used as parameters for measuring discomfort in sedated patients.

Discuss the administration of artificial hydration during CPS

Palliative sedation, when appropriately indicated and correctly used, does not seem to have any detrimental effect on patient survival.[5,80] However, one in four physicians estimated that CPS has shortened patients' life span (chapter 4). An explanation for this finding could be that physicians commonly have difficulty in estimating life expectancy and are often inclined to overestimate it.[81,82] Another explanation could be that there is actually a life-shortening effect of CPS. In our retrospective study 18% of patients had an intake of more than 500 mL the day before CPS started, and artificial hydration was continued or started in only 2.3% of the patients. In these patients, CPS without artificial hydration can have a life-shortening effect. It could be argued that artificial hydration is medically futile, hampers the natural dying process, and may result in additional suffering. The Dutch national guideline on palliative sedation also does not recommend artificial hydration during sedation in general, however, in patients who have considerable oral intake before the start of continuous sedation, physicians should explicitly discuss the issue of artificial hydration before the start of continuous sedation, or physicians should offer intermittent sedation.[1] When communicating with these patients one should discuss whether the application of artificial hydration during palliative sedation will improve the comfort of the sedated patient or not, and whether a possible life-shortening effect of CPS is acceptable if artificial hydration is not given.

Complement the Dutch national guideline on palliative sedation

The Dutch national guideline on palliative sedation recommends timely open communication between physicians and their patients about the realistic intentions, possibilities and limitations at the end of life.[1] However, in this guideline more attention should be given to the timely identification, communication and monitoring of patients at high-risk for CPS.

Furthermore, the Dutch national guideline emphasizes that agreements must be made regarding the observation points and times during CPS and about the factors that may lead to a review of the medication, but the guideline fails to describe how these efforts should be carried out.[1] The Dutch national guideline should be more explicit on which signs of discomfort during CPS must be looked for, including the individual items of the DS-DAT. Improving the recommendations should induce better symptom control and more stable unambiguous application of palliative sedation.[77] Additionally, the Dutch national guideline should include intermittent sedation as a precondition for the use of CPS for treating refractory existential suffering. This type of sedation is less far-reaching than the administration of CPS, and its use may prevent the eventual need for CPS for this type of suffering.

Table 1. Directions for clinical practice and health care policy

Monitor high-risk patients

In patients who use opioids or psycholeptics and in patients with feelings of hopelessness, extra screening for signs of opioid toxicity, the presence and intensity of delirium, pain, dyspnea and feelings of hopelessness should take place.

Inform high-risk patients[a] early in the palliative trajectory and motivate advance care planning

Inform high-risk patients about the indication and preconditions for CPS early in the palliative trajectory: communicate that CPS is a last resort intervention for refractory suffering, that the life expectancy of a patient may not exceed 2 weeks at the moment CPS is started and that CPS has to be distinguished from euthanasia. Enhance the patient's autonomy by establishing an end-of-life care plan that will meet the patient's goals, values, needs, and preference.

Fulfil the preconditions for CPS for patients with existential suffering

Before CPS is administered in patients with existential suffering, the following preconditions should be fulfilled: (1) an expert in psychosocial problems and meaning-of-life issues has been consulted; (2) intermittent sedation is initiated before CPS is attempted; (3) the patient has a life expectancy of a maximum of one to two weeks; (4) informed consent has been obtained; and (5) existential suffering is not the patient's sole refractory symptom.

Be aware of personal values in end-of-life care decision making

Physicians should be aware that there can be subjectivity in determining the refractoriness of symptoms and that their own values may enter into the decision making for CPS.

Inform patients and relatives of the effectiveness of CPS before starting and monitor patients during CPS

Communicate with patients and their relatives that CPS is in general a fast-acting and effective intervention but also that CPS is not a one-size-fits-all intervention. Therefore, monitoring of patient's discomfort during sedation is essential. Communicate prior to the start of CPS regarding which signs of discomfort are looked for during sedation, the individual items of the DS-DAT (e.g., facial expression, body language, fidgeting and negative vocalization) can be used as parameters.

Discuss the administration of artificial hydration during CPS

In patients with a considerable intake before the start of CPS, the physician should discuss whether the administration of artificial hydration during palliative sedation will improve the comfort of the sedated patient or not, and whether a possible life-shortening effect of CPS will be accepted if artificial hydration is not given.

Complement the Dutch national guideline on palliative sedation

The guideline should give more attention to the timely identification, communication with and monitoring of patients at high-risk for CPS and should be more explicit on which signs of discomfort during CPS must be looked for. Additionally, the guideline should include intermittent sedation as a precondition for the use of CPS for treating refractory existential suffering.

[a] High-risk patients are patients at younger ages, male patients, patients with a cancer diagnosis, patients with feelings of hopelessness, patients dying in a hospital, patients living in a French-speaking community setting in Belgium, patients who use opioids, and patients who use psycholeptics.

CPS = continuous palliative sedation; DS-DAT = Discomfort Scale–Dementia of Alzheimer Type

Implications for further research

Although the studies described in this thesis provide important insight into the determinants, practice and outcome of the administration of CPS, there are still several aspects that deserve more attention in future research. These themes are discussed below.

Determinants of CPS

This thesis revealed some patient-related determinants of CPS (chapters 2 and 3). However, the research in this thesis reported only individual factors, and these factors did not cover all domains of palliative care extensively. It is plausible that clinical practice is more complex and that multiple physical, psychosocial and spiritual problems are present and interact. Additionally, this thesis showed that the mechanisms of these determinants are unclear and that other determinants could be present. Therefore, future prospective multicenter research should be performed to confirm the determinants of CPS reported in this thesis, using clearly outlined and similar definitions of CPS within multivariate models. To determine if the use of opioids and psycholeptics are truly independent determinants or that other underlying factors are present, the symptoms pain, dyspnea and delirium should be included in the multivariate model. Moreover, such a multivariate model should include not only individual factors but also clusters, e.g., the symptoms pain and exhaustion. Additionally, to control for clustering of patients and to exclude confounding of characteristics of residence or health care providers, the residence should be included in the multivariate model. Besides, it is preferably to perform such research in different settings and countries, as "country" has also been found to be an important factor in predicting the probability of receiving sedation, suggesting that cultural, social, legal, and organizational factors probably play a role.[78] Furthermore, besides assessments at admission, assessments should also be performed during the whole admission at regular time intervals to determine whether the associations are time-sensitive. Finally, to determine if monitoring and appropriately applied interventions actually can alter the course of symptoms in high-risk patients and the patients' eventual need for palliative sedation, an interventional study should be performed in patients with clinically relevant determinants. Such research could also determine whether informing patients at high risk and their relatives about the indication and preconditions for CPS early in the palliative trajectory results in more effective communication at the moment refractory symptoms occur, and reduces concerns of relatives before and during the administration of CPS.

Observer-based scale to monitor discomfort during

The DS-DAT has the potential to be a useful scale for measuring comfort during CPS. However, before the DS-DAT can be used in clinical practice, further research on the psychometric properties of the DS-DAT is recommended. Such research should focus on the face validity of this tool, e.g., using the Delphi method. This effort should preferably be undertaken by a panel of experts from an internationally accepted organization, e.g., the European Association for Palliative Care. Only then is the widespread adoption by the palliative care community and implementation of a scale to monitor discomfort during the administration of CPS in clinical practice possible. Such a panel should discuss whether all the items of the DS-DAT are valid for measuring discomfort in sedated patients. For example, it is possible that an observer scores the item 'noisy breathing' in cases in which a 'death rattle' is present, whereas it is doubtful whether sedated patients actually experience discomfort from this symptom.[83] Additionally, the DS-DAT includes positive items (content facial expression and relaxed body language). The aim of CPS is providing comfort; therefore it seems reasonable to include these positive items. However, the question arises whether this inclusion corresponds with clinical practice. Do physicians and nursed focus on signs of discomfort rather than signs of comfort, and therefore can a decrease of discomfort be interpreted as an

increase of comfort? Furthermore, the DS-DAT records the frequency, intensity, and duration of each of the behavioral characteristics. As a result of this measurement a more specific score of the level of discomfort is possible. However, the question arises whether a score of three on one item is equal to a score of one on three items. Finally, such a panel should discuss whether some items of the DS-DAT deserve more weight or not in determining discomfort during the administration of CPS. Future research should also focus on the inter- and intrarater reliability of the DS-DAT in a population of sedated patients. Moreover, to obtain some concurrent validity, comparison between simultaneously assessments using the DS-DAT and subjective assessments by physicians and nurses should be performed. Additionally, establishing a cut-off point for the DS-DAT that reflects comfort in patients with CPS could be helpful to determine if CPS provides sufficient relief of discomfort. Although there is no cut-off point for the DS-DAT that reflects comfort in patients with CPS, a score of eight is mentioned as the cut-off point for high versus not high discomfort in a population of confused elderly patients or patients with dementia.[48,49] Future research should determine if a cut-off point can be established, although the interpretation of a (particular) score on an observational scale should not be separated from the subjective assessment of the health care provider. A score above a cut-off point could indicate that sedative dose escalation to alleviate discomfort is necessary. However, a score below a cut-off point may not always indicate that the patient is comfortable. Therefore, a clinical assessment by the physician or nurse should also always be performed. Finally, although it seems plausible that the use of an observational assessment instrument helps to ensure that the patient becomes comfortable while sedated, prevents unnecessary dose escalation and improves communication between health care providers and between professionals and the patients' families,[53,54] future research should also evaluate the impact of the use of the (revised) DS-DAT on these items. Some authors question the accuracy of observational scales in palliative patients because the ability to react with facial expressions or body movements may be diminished in the end-of-life stage.[84] What if unresponsiveness is not equal to unawareness?[45] Some authors therefore urgently recommend more research on the measurement of the level of awareness of patients who are continuously sedated until death by using electroencephalography derivates such as bispectral index (BIS), or on correlating BIS values with the clinical assessment of a physician.[7] However, besides the fact that BIS is an invasive technique, a recent publication shows that the wide range of BIS values in deeply sedated and comfortable patients seems to hamper the use of BIS in daily clinical practice.[84] Therefore, we have to rely on clinical assessments by physicians, nurses as well as relatives, in combination with observer-based scales such as the DS-DAT. Although the fact that the key notion 'sedated patients do not suffer' is never completely without doubt,[79] it does not mean that sedated terminal patients do suffer. With the lack of evidence about the capacity of sedated patients to suffer, we have to assume that a sedated patient who looks comfortable and is no longer conscious does not suffer. In the future, if the DS-DAT shows good psychometric properties and the palliative care community adopts the (revised version of the) DS-DAT as a scale for measuring comfort during CPS, attention should also be paid to the implementation of this scale. First, the DS-DAT is a relatively complex scale, especially the scoring of the intensity, duration, and the number of items,[85] therefore, training and regular use of this scale are required. Second, recommendations regarding which discipline should perform the assessment should be made. Although many disciplines may be involved in the administration of CPS, nurses often play a critical role in the observations and in the communication with relatives during CPS, and they seem to be the most suitable assessor. Third, these recommendations should also include what adequate time intervals for monitoring are, e.g., at least twice a day with closer intervals of 30 to 60 minutes during the initiation of CPS until adequate comfort is achieved.

Determinants of discomfort during CPS

The results presented in this thesis showed that an intake of at least a small amount of fluid before sedation, the presence of the refractory symptom vomiting and the presence of multiple refractory symptoms were positively associated with a higher mean score on the DS-DAT during the last eight hours of life. Other characteristics, e.g., duration of CPS, gender, age, pain, dyspnea and delirium were not significantly associated. These results are in line with the findings of a previous prospective study.[30] However, a previous retrospective study reported contrasting findings regarding intake, duration and the presence of the refractory symptom vomiting.[86] Therefore, the results presented in this thesis must be viewed as a first step in the identification of patients at risk for discomfort during CPS and could be supportive for future research.

Euthanasia

The research presented in this thesis showed that close to one in five sedated patients with cancer had made a previous request of euthanasia (chapter 4). Additionally, having a previous request for euthanasia is significantly associated with the administration of CPS for existential suffering (chapter 5). These findings might indicate that CPS is used in these cases as an alternative to euthanasia. It has been suggested that physicians sometimes are vague towards patients regarding the possibility of euthanasia early in the palliative trajectory, telling patients later in the final phase of life that it is too late to initiate the procedures for euthanasia and then opting for CPS.[87] Research also shows that some physicians choose CPS above euthanasia because 'the best part is that you do not have to have anything arranged and it's just always possible.'[88] However, careful interpretation of the findings presented in this thesis is warranted. We did not ask physicians why a previous request for euthanasia was not granted. Plausible reasons for denying such a request could be present.[21,69,89,90] There could be a lack of time to complete the euthanasia process: the patient could have postponed the formal euthanasia request until it was too late or the dying process could have been short. Additionally, the patient could have lost mental capacity during the formal euthanasia process. Moreover, requests for euthanasia are often made in advance.[91] Such a request early in the palliative trajectory could be made to keep in control, but could disappear at the end of life. Future research should illuminate the reasons behind decisions not to grant requests for euthanasia and to administer CPS instead.

Existential suffering

Elderly care physicians often mention existential suffering and loss of dignity as an indication for CPS (chapter 4). However, the refractoriness of this type of suffering was not determined by investigating the etiology of each type of suffering, what types of treatment had been attempted, and how symptoms were recognized (especially in patients with dementia). Furthermore, in almost all cases refractory existential suffering occurs in conjunction with refractory physical symptoms. We did not determine what impact each of the symptoms had on the decision to administer CPS. It is possible that nonphysical symptoms may have exacerbated physical symptoms and could have compromised the patient's endurance, without being the decisive refractory symptom. Further research is therefore needed on when, how, and by whom existential suffering at the end of life should be best treated. Research should also determine how existential suffering affects or is affected by other symptoms patients may be experiencing, and to clarify the impact of existential suffering on the decision to administer CPS.[64]

Medication scheme of the national guideline for palliative sedation

The dose range and the mean dose of midazolam (chapter 4) was consistent with the recommendations of the Dutch national guideline.[1] However, little is known about the pharmacokinetics of midazolam in a frail, elderly population, and the recommendations of the guideline are based on level three or four evidence, i.e., expert opinion and non-comparative studies. Furthermore, recently some comments on the revised medication table of the national guideline have been made.[92,93] Therefore, further research is needed to establish the optimal medication scheme for CPS and to support the medication recommendations of the RDMA guideline. Such research should focus on which drugs are stopped at the start of CPS and which drugs are started, which doses are used and at what time intervals dose and drugs adjustments are required during CPS.

Conclusions

This thesis showed that CPS decreases the level of discomfort within an acceptable timeframe and appears to be an effective intervention for refractory symptoms in the final days of a patient's life. However, the administration of CPS should be considered as a palliative intervention of last resort. Additionally, CPS is not a one-size-fits-all intervention because some sedated patients still experienced higher levels of discomfort in the last hours of life.

Therefore, both in clinical practice as well as in the national guideline on palliative sedation, more awareness for monitoring for signs of opioid toxicity, the presence and intensity of delirium, pain, dyspnea and feelings of hopelessness should be present in patients in the palliative trajectory. Adequate palliative care with careful assessment of potential reversible factors and non-sedating interventions should be the cornerstone of treatment before starting palliative sedation. Effective interventions in these patients could possibly prevent a refractory state for such symptoms, thereby possibly limiting the future need for CPS. Moreover, advance care planning and information on the indication and the preconditions of CPS early in the palliative trajectory are advisable in high-risk patients. This approach may prevent unforeseen situations and difficulties in communication at the bedside when problems arise.

Furthermore, more attention should be paid to the suggested preconditions for administering CPS in cases in which existential suffering becomes an indication for CPS, especially the use of intermittent sedation and consultation with a palliative care consultant or spiritual counsellor. Additionally, in patients who have considerable oral intake before the start of continuous sedation, physicians should at least explicitly discuss the issue of artificial hydration and the possible concomitant life-shortening effect of CPS, or preferably should offer intermittent sedation.

Finally, if an indication arises for the administration of CPS, it is important to communicate prior to the start of CPS which signs of discomfort are looked for during sedation. Currently, there is no validated and generally accepted scale for monitoring discomfort in sedated patients. Although further research on the psychometric properties of the DS-DAT is needed before this tool can be used in clinical practice, the individual items of this scale, e.g., facial expression, body language, fidgeting and negative vocalization, can already be used as parameters in clinical practice.

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Summary

Summary

Palliative sedation is defined as "the deliberate lowering of a patient's level of consciousness in the last stages of life." The objective of palliative sedation is to alleviate the patient's discomfort caused by symptoms that do not respond (fast enough) to conventional modes of treatment and/or if these modes of treatment are accompanied by unacceptable side-effects, so-called refractory symptoms. The term "palliative sedation" encompasses two distinct types of intervention: brief or intermittent sedation and continuous sedation administered until death (CPS).

Although CPS is increasingly accepted as part of medical practice, it is also considered as a last resort intervention. CPS not only takes away a patient's suffering but also produces an impaired capacity to communicate, which takes away any potential positive and meaningful experiences a patient might have. In the last two decades, more and more attention has been paid to this intervention in the literature, and in 2005, the Royal Dutch Medical Association (RDMA) described the conditions in which palliative sedation is good medical practice in a national guideline. Although the RDMA guideline gave a comprehensive framework for clinical decision-making and the administration of CPS, and literature provided more insight, it could not solve all the problems or answer all the questions regarding the increasing administration of CPS. First, little is known about the early identification of patients at high risk for CPS. The identification of these determinants could improve advance care planning and quality of life for high-risk patients in a terminal phase. Second, little insight has been achieved into the practice of CPS by elderly care physicians in general and into the administration of CPS for existential suffering in particular. More insight is essential to contribute to the further development of guidelines and clinical practice. Finally, although the RDMA guideline states that monitoring of (continuous) palliative sedation is essential, the "how" of monitoring of the level of suffering during (continuous) palliative sedation is currently an open question. Accordingly, little is known about the efficacy of CPS and determinants of inadequate symptom relief during CPS. Therefore, the aim of this thesis was to provide more insight into these topics (***chapter 1***).

In ***chapter 2***, we provide a systematic review of PubMed, EMBASE, and CINAHL on determinants of CPS. In total, eight papers fulfilled the inclusion criteria. The following nine factors were found to be associated with the administration of CPS: younger age, male sex, having cancer, feelings of hopelessness, dying in a hospital, living in a Dutch speaking community setting in Belgium, very nonreligious or extremely nonreligious physicians, physicians working in "other hospital" specialties, and physicians in favor of assisted death. Given the variation in study designs and the limitations of the included studies, the outcomes should be interpreted carefully. This review highlighted the need for further research, particularly regarding factors that can be influenced and that may alter the course of a patient's symptoms and the patient's eventual need for palliative sedation.

A prospective multicenter observational study was performed in six Dutch hospices and three nursing home-based palliative care units to explore which patient-related factors at admission are associated with receiving CPS later in the terminal phase of life (***chapter 3***). The following variables were analyzed: age, gender, diagnosis, use of opioids or psycholeptics, number of medications, Karnofsky performance status scale score, Edmonton symptom distress score and Glasgow coma scale score. Our findings showed that

only the use of opioids at admission was independently associated with the administration of CPS. In this group of high-risk patients, a comprehensive personalized care plan starting at admission is mandatory. This chapter shows that further research to identify other determinants of the administration of CPS and to investigate which early interventions will be effective to prevent the need for CPS in patients at high risk is needed.

In ***chapter 4***, we investigated the practice of CPS by Dutch elderly care physicians. One thousand two hundred fifty-four registered members of the Dutch Association of Elderly Care Physicians and Social Geriatricians received a structured questionnaire concerning their last case of CPS. A total of 675 physicians responded (response rate 54%), and 316 patients were described. The majority of these patients had cancer or dementia. In almost all cases, symptom relief was the aim, and in close to one in five patients with cancer, a previous request for euthanasia had been reported. In addition to physical symptoms, anxiety, exhaustion, loss of dignity, and existential distress were often mentioned as refractory symptoms in the decision to start CPS by elderly care physicians. The dosage range of midazolam, the most frequently used drug in this study, fits the recommendations of the Dutch national guideline on palliative sedation. This chapter shows a need for prospective research about the acceptability and assessment of nonphysical symptoms as indications for CPS and about the reasons not to grant a preceding euthanasia request.

Some guidelines and recommendations identify existential suffering as a potential refractory symptom for which CPS can be administered under certain conditions. To provide insight into this specific indication for CPS, a subanalysis of the results of the questionnaire was performed (***chapter 5***). Existential suffering was a refractory symptom in 83 of the patients. For most of the patients with refractory existential suffering, other refractory symptoms were also reported, and the life expectancy was seven days or less; informed consent for initiating CPS had been obtained in all cases. Consultation and intermittent sedation before the start of CPS were far less frequently reported than one would expect based on the preconditions mentioned in guidelines and recommendations. Multivariate analysis showed that being male, having previously requested euthanasia, having a nervous system disease, or having an "other diagnosis" were positively correlated with the administration of CPS for existential suffering. We conclude that more attention should be paid to the suggested preconditions and to the presence of existential suffering in male patients or patients with a nervous system disease.

In ***chapter 6***, we present a prospective observational multicenter study in nine hospices and palliative care units, to observe the course of discomfort in sedated patients and to identify determinants of discomfort during CPS. For monitoring of patient discomfort before and during CPS, the Discomfort Scale–Dementia of Alzheimer Type (DS-DAT) was independently assessed, and we compared the mean group score of discomfort between four predefined timeframes of CPS. A total of 130 patients were sedated, and the DS-DAT was completed in 106 patients at least once. This study showed that discomfort significantly decreased within 8 hours after the start of CPS and remained relatively stable until the moment of death. The patient's intake of a small amount of fluid or more before CPS, the presence of vomiting or multiple symptoms were positively associated with a higher mean score of the DS-DAT during the last eight hours of life. This study shows that CPS is associated with a decrease in the level of discomfort within an acceptable timeframe, although in some sedated patients higher levels of discomfort in the last hours of life occurred. Although the DS-DAT seems to be of value for monitoring the level of discomfort during CPS, the results of this study should be interpreted within the constraints of the limitations, and further research on the psychometric properties of this tool is needed before the DS-DAT can be used in clinical practice.

The main findings of this thesis as well as the methodological considerations and implications for clinical practice and future research are discussed in ***chapter 7***. This thesis showed that CPS decreases the level of discomfort within an acceptable timeframe and appears to be an effective intervention for refractory symptoms in the final days of a patient's life. However, the administration of CPS should be considered as a palliative intervention of last resort. Additionally, CPS is not a one-size-fits-all intervention because some sedated patients still experienced higher levels of discomfort in the last hours of life. Therefore, both in clinical practice as well as in the national guideline on palliative sedation, more awareness for monitoring for signs of opioid toxicity, the presence and intensity of delirium, pain, dyspnea and feelings of hopelessness should be present in patients in the palliative trajectory. Adequate palliative care with careful assessment of potential reversible factors and non-sedating interventions should be the cornerstone of treatment before starting palliative sedation. Effective interventions in these patients could possibly prevent a refractory state for such symptoms, thereby possibly limiting the future need for CPS. Moreover, advance care planning and information on the indication and the preconditions of CPS early in the palliative trajectory are advisable in high-risk patients. This approach may prevent unforeseen situations and difficulties in communication at the bedside when problems arise.

Furthermore, more attention should be paid to the suggested preconditions for administering CPS in cases in which existential suffering becomes an indication for CPS, especially the use of intermittent sedation and consultation with a palliative care consultant or spiritual counsellor. Additionally, in patients who have considerable oral intake before the start of continuous sedation, physicians should at least explicitly discuss the issue of artificial hydration and the possible concomitant life-shortening effect of CPS, or preferably should offer intermittent sedation.

Finally, if an indication arises for the administration of CPS, it is important to communicate prior to the start of CPS which signs of discomfort are looked for during sedation. Currently, there is no validated and generally accepted scale for monitoring discomfort in sedated patients. Although further research on the psychometric properties of the DS-DAT is needed before this tool can be used in clinical practice, the individual items of this scale, e.g., facial expression, body language, fidgeting and negative vocalization, can already be used as parameters in clinical practice.

Samenvatting

Samenvatting

Onder palliatieve sedatie wordt verstaan "het opzettelijk verlagen van het bewustzijn van een patiënt in de laatste levensfase". Het doel van palliatieve sedatie is het verlichten van het lijden van de patiënt, veroorzaakt door de aanwezigheid van één of meer refractaire symptomen. Een symptoom is of wordt refractair als geen van de conventionele behandelingen (voldoende snel) effectief zijn en/of deze behandelingen gepaard gaan met onaanvaardbare bijwerkingen. De term palliatieve sedatie omhelst twee verschillende vormen: kortdurend of intermitterend sederen en continu sederen tot het moment van overlijden (CPS).

Hoewel CPS in toenemende mate wordt geaccepteerd als een mogelijke interventie binnen het normaal medisch handelen, wordt CPS ook gezien als laatste redmiddel. CPS neemt niet alleen het lijden van de patiënt weg, maar zorgt ook voor een vermindering van de communicatieve vaardigheden. Hierdoor wordt de mogelijkheid bij de patiënt om potentieel positieve en betekenisvolle ervaringen te hebben weggenomen. In de laatste twee decennia is in de literatuur steeds meer aandacht gegeven aan deze interventie. Ook heeft de Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst (KNMG) in 2005 een richtlijn opgesteld waarin beschreven wordt wanneer palliatieve sedatie medisch gezien verantwoord is. Ondanks dat de KNMG richtlijn de indicatiestelling, de randvoorwaarden, het besluitvormingsproces en de uitvoering van palliatieve sedatie beschrijft en de literatuur steeds meer inzicht in de toepassing van CPS geeft, blijven in de praktijk nog vragen en knelpunten aanwezig over deze in toenemende mate toegepaste interventie. Ten eerste is weinig bekend over de vroegtijdige identificatie van hoog-risico patiënten voor de toepassing van CPS. De identificatie van dergelijke determinanten kan ervoor zorgen dat het verrichten van advance care planning bij hoog-risico patiënten verbetert, alsook hun kwaliteit van leven en sterven. Ten tweede is weinig bekend over de praktijk van de toepassing van CPS door specialisten ouderengeneeskunde in het algemeen en over de toepassing van CPS voor existentieel lijden in het bijzonder. Meer inzicht hierover geeft een belangrijke bijdrage aan de doorontwikkeling van richtlijnen en het verbeteren van het klinisch handelen in de dagelijkse praktijk. Als laatste, de KNMG richtlijn palliatieve sedatie beschrijft dat het monitoren van (continue) sedatie essentieel is, echter de wijze waarop het monitoren van lijden gedurende (continue) sedatie dient plaats te vinden blijft een open vraag. Hierdoor is weinig bekend over de effectiviteit van CPS en over determinanten van ontoereikende klachtenbestrijding gedurende CPS. Het doel van dit proefschrift was dan ook om meer inzicht in deze onderwerpen te verschaffen (***hoofdstuk 1***).

In ***hoofdstuk 2*** wordt de uitkomst van een systematische review over determinanten van CPS beschreven. Deze review werd verricht met behulp van de zoeksystemen PubMed, EMBASE, en CINAHL. Acht artikelen voldeden aan de inclusiecriteria. De volgende negen factoren welke geassocieerd zijn met de toepassing van CPS werden gevonden: jongere leeftijd, mannelijk geslacht, het hebben van kanker, de aanwezigheid van gevoelens van hopeloosheid, het overlijden in een ziekenhuis, het woonachtig zijn in een Nederlands sprekende gemeenschap in België, de aanwezigheid van erg niet-religieuze of zeer niet-religieuze artsen, de aanwezigheid van artsen

werkzaam in een "ander" ziekenhuisspecialisme en de aanwezigheid van artsen welke voorstander zijn van hulp bij zelfdoding. Door de variatie in onderzoeksdesign en de beperkingen van de geïncludeerde studies dienen de resultaten van deze review met enige voorzichtigheid te worden geïnterpreteerd. Deze review laat zien dat nieuw onderzoek nodig is, met name naar factoren welke beïnvloed kunnen worden. Beïnvloeding van dergelijke factoren kan het beloop van de symptomen bij de patiënt veranderen, waardoor mogelijk ook de uiteindelijke noodzaak van de toepassing van CPS voorkomen kan worden.

In zes hospices en drie palliatieve units van verpleeghuizen in Nederland werd een prospectief observationeel multicenter onderzoek verricht. Een doel van dit onderzoek was het exploreren welke patiëntgebonden factoren bij opname geassocieerd zijn met de toepassing van CPS in de laatste fase van het leven (***hoofdstuk 3***). De volgende variabelen werden geanalyseerd: leeftijd, geslacht, diagnose, gebruik van opioïden, gebruik van psycholeptica, aantal medicijnen, Karnofsky performance status scale score, Edmonton symptom distress score en Glasgow coma scale score. De resultaten laten zien dat enkel het gebruik van opioïden bij opname onafhankelijk geassocieerd is met de toepassing van CPS. In deze hoog-risico patiënten is reeds bij opname een uitgebreid persoonlijk zorgplan nodig. Dit hoofdstuk laat verder zien dat meer onderzoek nodig is om andere determinanten te identificeren en om te onderzoeken of vroegtijdige interventies bij deze hoog-risico patiënten effectief zijn in het voorkomen van de noodzaak van de toepassing van CPS.

Hoofdstuk 4 beschrijft het onderzoek naar de praktijkvoering van CPS onder specialisten ouderengeneeskunde. Een gestructureerde enquête, met vragen over de laatste patiënt waarbij CPS werd toegepast, werd gestuurd naar 1254 leden van de vereniging van specialisten ouderengeneeskunde en sociaal geriaters. In totaal reageerden 675 artsen (respons 54%) en 316 patiënten werden beschreven. De meeste patiënten hadden kanker of dementie. In bijna alle casus was symptoombestrijding het doel van CPS. In bijna 1 op de 5 patiënten met kanker werd melding gedaan van een voorgaand euthanasieverzoek. Naast refractaire lichamelijke symptomen werden door specialisten ouderengeneeskunde ook refractaire symptomen als angst, uitputting, verlies van waardigheid en existentieel lijden benoemd als indicatie voor CPS. Midazolam was het meest gebruikte middel in deze studie en de genoemde doseringen komen overeen met de aanbevelingen van de landelijke KNMG richtlijn palliatieve sedatie. Dit hoofdstuk laat de noodzaak zien voor prospectief onderzoek. Met dergelijk onderzoek kan inzicht verkregen worden over de wijze waarop niet-lichamelijke klachten in kaart gebracht worden, over de aanvaardbaarheid van dergelijke klachten als indicatie voor CPS en de achterliggende redenen om een voorgaand euthanasieverzoek niet in te willigen.

Sommige richtlijnen en aanbevelingen benoemen existentieel lijden als een potentieel refractair symptoom, waarvoor onder bepaalde voorwaarden CPS gegeven kan worden. Om meer inzicht te krijgen in deze specifieke indicatie voor CPS werd een subanalyse van de resultaten van het enquête onderzoek verricht (***hoofdstuk 5***). Existentieel lijden was een refractair symptoom bij 83 patiënten. Bij de meeste patiënten met existentieel lijden werd ook de aanwezigheid van andere refractaire symptomen beschreven en was de levensverwachting zeven dagen of minder. Bij alle patiënten was informed consent verkregen voor de start van CPS. Consultatie en het gebruik van intermitterende sedatie voor de start van CPS werden beduidend minder frequent beschreven dan verwacht zou worden op basis van de voorwaarden genoemd in richtlijnen en aanbevelingen. Multivariate analyse

laat zien dat het hebben van het mannelijke geslacht, een voorgaand euthanasieverzoek, een ziekte van het zenuwstelsel of een "andere" diagnose positief gecorreleerd zijn met de toepassing van CPS voor existentieel lijden. Meer aandacht dient uit te gaan naar de voorwaarden voor CPS bij deze indicatie en naar de aanwezigheid van existentieel lijden bij mannelijke patiënten en bij patiënten met een ziekte van het zenuwstelsel.

In ***hoofdstuk 6*** wordt het prospectief observationeel multicenter onderzoek beschreven, waarin gekeken is naar het beloop van discomfort in gesedeerde patiënten en naar determinanten van discomfort tijdens de toepassing van CPS. Het onderzoek heeft plaatsgevonden in negen hospices en palliatieve units.
De Discomfort Scale–Dementia of Alzheimer Type (DS-DAT) werd onafhankelijk afgenomen om de mate van discomfort voor en tijdens de toepassing van CPS te meten. De gemiddelde groepsscore van de DS-DAT tussen vier vooraf gedefinieerde tijdframes werd vergeleken. In totaal werd bij 130 patiënten CPS toegepast en werd bij 106 patiënten ten minste 1 meting van de DS-DAT verricht. De mate van discomfort daalde significant binnen 8 uur na de start van de sedatie en bleef aansluitend relatief stabiel tot aan het moment van overlijden. Een intake van een kleine hoeveelheid vocht of meer en de aanwezigheid van het symptoom braken of meerdere symptomen waren positief geassocieerd met een hogere gemiddelde score van de DS-DAT in de laatste acht uur van het leven. Deze studie laat zien dat de toepassing van CPS is geassocieerd met een verlaging van de mate van discomfort binnen een acceptabel tijdsbestek, alhoewel in de laatste uren van het leven bij sommige patiënten ook hogere scores van discomfort aanwezig waren. De DS-DAT lijkt van toegevoegde waarde om de mate van discomfort te monitoren gedurende CPS, echter de resultaten van deze studie dienen in het licht van de beperkingen van het onderzoek gezien te worden. Voordat de DS-DAT in de praktijk gebruikt kan worden, is verder onderzoek naar de psychometrische eigenschappen van deze schaal nodig.

De hoofdresultaten van dit proefschrift, de methodologische overwegingen en de implicaties voor de praktijk en toekomstig onderzoek worden bediscussieerd in ***hoofdstuk 7***. Dit proefschrift laat zien dat de toepassing van CPS een verlaging van de mate van discomfort geeft binnen een acceptabel tijdsbestek. CPS lijkt dan ook een effectieve interventie voor refractaire symptomen in de laatste dagen van het leven van een patiënt. Daarentegen dient CPS gezien te worden als laatste redmiddel en lijkt het niet een one-size-fits-all interventie, aangezien bij sommige gesedeerde patiënten nog steeds hogere scores van discomfort in de laatste uren van het leven worden gezien. Om deze reden dient zowel in de praktijk als in de landelijke richtlijn palliatieve sedatie meer bewustwording te komen voor het monitoren van tekenen van opiaatintoxicatie en de aanwezigheid van delier, pijn, dyspneu en gevoelens van hopeloosheid bij patiënten in de palliatieve fase. Voordat CPS wordt toegepast, dient adequate palliatieve zorg te worden gegeven, waarbij actief gezocht wordt naar reversibele oorzaken van klachten en waarbij niet sederende interventies worden ingezet. Effectieve interventies kunnen mogelijk het ontstaan van refractaire symptomen voorkomen, waardoor de noodzaak voor de toepassing van CPS mogelijk minder vaak aanwezig is. Bovendien is advance care planning en het geven van informatie over de indicatie en voorwaarden van CPS vroegtijdig in het palliatief traject aan te bevelen. Een dergelijke aanpak kan mogelijk onvoorziene situaties en problemen in de communicatie, op het moment dat problemen ontstaan, voorkomen.

Tevens dient meer aandacht te worden geschonken aan de voorgestelde voorwaarden voor de toepassing van CPS op het moment dat existentieel lijden de indicatie gaat vormen. Het gaat dan met name om de voorwaarde van het toepassen van intermitterende sedatie en het consulteren van een palliatief consulent of spiritueel verzorger voorafgaand aan CPS. Verder dient bij patiënten met een aanzienlijke intake voor de start van CPS het mogelijk levensbekortend effect van CPS en de voor- en nadelen van kunstmatige vochttoediening tijdens CPS te worden besproken, of dient bij voorkeur intermitterende sedatie te worden gegeven.

Tot slot is het belangrijk dat als een indicatie voor de toepassing van CPS ontstaat, reeds voor de start van CPS te bespreken naar welke signalen van discomfort wordt gekeken gedurende de sedatie. Momenteel is nog geen gevalideerde en geaccepteerde schaal voor het monitoren van discomfort in gesedeerde patiënten aanwezig. Ondanks dat verder onderzoek naar de psychometrische eigenschappen van de DS-DAT nodig is voordat deze in de praktijk gebruikt kan worden, kunnen de individuele items van deze schaal al wel als parameters gebruikt worden. Hierbij kan gedacht worden aan de items gelaatsuitdrukking, lichaamstaal, bewegingsonrust en negatief stemgebruik.

Dankwoord

Dankwoord

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Curriculum vitae

Curriculum vitae

Rogier van Deijck (16 maart 1972) is geboren en getogen in Breda en haalde in 1990 daar zijn Atheneum-B diploma aan de Nassau Scholengemeenschap. In hetzelfde jaar startte hij met de studie geneeskunde aan de Katholieke Universiteit Nijmegen. In 1998 behaalde hij zijn artsexamen. In afwachting van de start van de vervolgopleiding tot huisarts ging hij werken bij De Zorggroep, destijds de Professor Dubois Stichting geheten. Tijdens de werkzaamheden in het verpleeghuis ontstond zijn interesse in de palliatieve zorg en het multidisciplinair werken. Het deed hem besluiten om de switch te maken naar het volgen van de opleiding tot verpleeghuisarts aan de Katholieke Universiteit Nijmegen. Deze opleiding voltooide hij in 2002, sindsdien is hij als specialist ouderengeneeskunde bij De Zorggroep werkzaam.

Hij heeft zich verder ontwikkeld op het gebied van de palliatieve zorg middels de kaderopleiding palliatieve zorg aan de Vrije Universiteit en de Universiteit van Amsterdam te Amsterdam. Deze opleiding heeft hij in 2007 met goed gevolg afgerond. Naast de werkzaamheden als arts voor mensen in de palliatieve fase, is hij ook als consulent bij het Integraal Kankercentrum Nederland en het Transmuraal Palliatief Team Noord-Limburg werkzaam. Ook was hij betrokken bij het maken van diverse richtlijnen op het gebied van palliatieve zorg. Een richtlijn waar hij ruim 11 jaar bij betrokken is geweest, is de richtlijn palliatieve sedatie van de Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst.

In 2009 is hij gestart met zijn promotieonderzoek met palliatieve sedatie als onderwerp, onder begeleiding van Prof. Dr. R.T.C.M Koopmans, Prof. Dr. K.C.P. Vissers, Dr. C.A.H.H.V.M. Verhagen en Dr. G.J. Hasselaar. Van dit onderzoek wordt verslag gedaan in het proefschrift dat voor u ligt. Hij hoopt na afronding van zijn promotie de vruchtbare samenwerking voort te zetten, om zo de nog aanwezig data van het prospectieve gedeelte van zijn onderzoek openbaar te maken. Daarnaast hoopt hij weer meer tijd vrij te kunnen maken voor de patiëntenzorg.

Rogier van Deijck is sinds 1998 getrouwd met Ans Gielen, samen hebben ze 3 kinderen: Tom (1999), Anne (2001) en Bas (2002).

List of publications

List of publications

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